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THE EFFECT OF TUBERCULOSIS ON THE SEROLOGICAL REACTIONS FOR SYPHILIS[1]

THOMAS PARRAN[2] AND KENDALL EMERSON[3]

The degree to which tuberculosis, or any severe metabolic disturbance, may influence the reliability of serodiagnostic tests for syphilis is a question which will probably require periodic study in order that the information may be kept abreast of the improvements in technical methods and the definite trend toward increasing the sensitivity of the procedures. The present study is the first of a proposed group designed to survey the general field of tuberculosis with regard to the possibility that this toxaemia adversely influences the specificity of carefully conducted serological tests for syphilis.

The study was participated in by five serologists[4] who have developed individual serodiagnostic tests. The clinical material was contributed by nine tuberculosis sanatoria[4] recommended by the National Tuberculosis Association, and the organization of the work was under the guidance of the Committee on Evaluation of Serodiagnostic Tests for Syphilis.[4]

A review of the literature reveals many reports which are difficult of appraisal because of the lack of knowledge on the part of the reviewer of the threshold of the serological test employed. The term "Wassermann test" has become a generic one, the use of which in the discussion of a particular technique does not convey definite information concerning the sensitiveness of the method in question. Also, improvements in technical methods make it extremely difficult to compare older reports with modern studies. The entire situation is probably best summed up by Stokes (1) when he places tuberculous disease in a "disputed" group as to its influence on the specificity of serodiagnostic tests.

Dulaney (2) found eight positive Wassermann reactions among one

[1] By special arrangement with the Editor, this paper is being published simultaneously in Venereal Disease Information.

[2] Surgeon General, United States Public Health Service.

[3] Managing Director, National Tuberculosis Association.

[4] See pages 7 and 8.

hundred tuberculous patients but did not say whether or not the patients had syphilis. Kilduffe and Hersohn (3) using a Kolmer complement fixation and a micro-Kline test did not find any false-positive reactions in a group of two hundred tuberculous individuals. Stucky and Huntley (4) concluded that the Kahn test was not adversely affected by the presence of tuberculous disease. Bowman (5) concluded that the incidence of positive Wassermann reactions was no more frequent among tuberculous patients than in the general population and Horowitz (6) found that the Wassermann test was as reliable in tuberculous as in nontuberculous individuals. A similar conclusion was arrived at by Snow and Cooper (7) when noncholesterinized antigens were used but they found 31 per cent of cases giving ± to ++ reactions with a cholesterinized antigen.

METHODS

Patients considered suitable for this study were selected by the clinical staffs of the coöperating sanatoria. Only white patients with moderately advanced or far advanced pulmonary disease, with or without fever, were chosen. Insofar as possible the presence of dual infection (syphilis and tuberculosis) was excluded by a detailed survey of the history and the clinical record of the donor. Comparable blood specimens from each acceptable donor were sent to the laboratories of the participating serologists. Two complement fixation tests (Kolmer and Eagle), four diagnostic flocculation tests (Eagle macroflocculation, Hinton, Kahn standard and Kline diagnostic) and two supersensitive flocculation tests (Kahn presumptive and Kline exclusion) were carried out with the blood of each donor, each test being performed in the laboratory of its originator. In cases which revealed any appreciable degree of serological discrepancy (among the laboratory reports) a recheck blood specimen was distributed and a detailed clinical resurvey of the donor as to the possibility of dual infection was carried out.

Each sanatorium contributed sera from approximately fifty tuberculous donors and, in addition, ten to fifteen specimens from known cases of syphilis. The blood specimens from the syphilitic donors were indiscriminately included in the shipments of blood from tuberculous donors in order that definitely positive serological findings might be encountered in the laboratories at frequent intervals during the study. The results of the tests with these specimens are not included in the final tabulations. Code letter and number were used for the identification of

specimens. A clinical record was prepared for each tuberculous donor detailing the extent of pulmonary involvement, presence or absence of temperature elevation, complication, etc. A complete clinical record as regards syphilis was prepared for all cases in which serological discrepancies occurred and in which it became necessary to establish the syphilis status of the patient as completely as possible. All reports and records were collected and tabulated at a central point.

COMMENT

From the original 458 supposedly nonsyphilitic tuberculous donors contributed by the nine sanatoria the sera of eight were found to be positive to many laboratory tests. In four of this group a close review

TABLE 1

Results obtained in sera from tuberculous donors

NAME OF TEST	PERCENTAGE SENSITIVITY 1938*	TUBERCULOUS DONORS		
		Sera tested	Number doubtful	Number positive
Kolmer complement fixation	78.2	441	0	0
Kahn standard	70.5	444	0	0
Eagle macroflocculation	71.0	430	0	1
Kahn presumptive	79.9	441	1	1
Kline diagnostic	73.4	439	4	0
Eagle complement fixation	72.2	419	10	1
Hinton flocculation	83.9	429	8	4
Kline exclusion	83.3	426	11	5

* Evaluation of Serodiagnostic Tests for Syphilis—1938.

of the patients' histories revealed evidence which supported the probable presence of syphilitic infection. Three of the remainder were not available for reëxamination, while in the remaining one the recheck failed to reveal history or clinical evidence indicative of syphilis. As this case was strongly positive to all tests on both original and recheck examination and as this number of unrecognized and unsuspected syphilitic infections in a group of this size is within the normal expectancy, it seems justifiable to omit the entire group of eight cases from the final tabulation.

In table 1 are displayed the results obtained in sera from tuberculous donors considered suitable for the purpose of the study. In considering this table it may be remarked that communications from some of the serologists called attention to the atypical nature of many of these adverse results.

TABLE 2

Results of serodiagnostic tests of sera from cases in which first specimens gave discrepant results

ORIGINAL NUMBER	SEX	COLOR	AGE	TUBERCULOSIS STAGE	FEBRILE OR AFEBRILE	EAGLE COMPLEMENT FIXATION		KOLMER COMPLEMENT FIXATION		EAGLE MACROFLOCCULATION		KAHN STANDARD		KLINE DIAGNOSTIC		HINTON FLOCCULATION		KAHN PRESUMPTIVE		KLINE EXCLUSION		RECHECK NUMBER
						Original	Recheck	Original	Recheck	Original	Recheck	Original	Recheck	Original	Recheck	Original	Recheck	Original	Recheck	Original	Recheck	
122-P	M	W	58	m	a	+	±	−	−	−	−	−	−	−	−	−	−	−	−	−	−	122-P
131-P	M	W	22	m	a	−	−	−	−	−	−	−	−	−	−	±	−	−	−	±	−	131-P
262-P	M	W	34	f	a	0	−	−	−	−	−	−	−	±	−	−	−	−	−	+	±	283-P
303-P	M	W	39	f	f	−	−	−	−	+	−	−	−	±	−	+	±	+	+	+	±	385-P
312-P	M	W	21	m	a	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	380-P
329-P	M	W	39	f	f	−	−	−	−	−	−	−	−	−	−	−	−	−	−	±	−	383-P
354-P	M	W	38	f	a	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	±	384-P
433-P	M	W	34	f	a	−	−	−	−	−	−	−	−	−	−	−	−	−	−	±	±	480-P
531-P	F	W	27	f	f	−	−	−	−	−	−	−	−	−	−	+	−	−	−	−	−	580-P
533-P	F	W	33	f	a	−	−	−	−	−	−	−	−	−	−	±	−	−	−	±	−	581-P
550-P	M	W	21	f	a	±	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	582-P
568-P	M	W	56	f	f	−	−	−	−	−	−	−	−	±	−	−	−	−	−	+	−	583-P
607-P	F	W	26	f	f	−	−	−	−	−	−	−	−	−	−	±	−	−	−	−	−	684-P
612-P	F	W	38	f	f	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	683-P
617-P	F	W	42	f		±	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	681-P
635-P	M	W	61	m	f	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	680-P
637-P	M	W	25	f	a	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	682-P
641-P	M	W	33	f	a	−	−	−	−	−	−	−	−	−	−	−	−	−	−	±	−	685-P
726-P	M	W	58	m	a	−	−	−	−	−	−	−	−	−	−	+	−	−	−	+	−	780-P
810-P	M	W	32	m	a	−	−	−	−	−	−	−	−	±	−	−	−	−	−	+	±	880-P
813-P	M	W	22	f	a	−	−	−	−	−	−	−	−	−	−	±	−	−	+	−	±	881-P
827-P	F	W	19	f	a	−	−	−	−	−	−	−	−	−	−	±	−	−	+	±	±	882-P
831-P	F	W	54	m	a	−	−	−	−	−	−	−	−	0	−	−	−	−	−	0	−	883-P
841-P	F	W	20	f	f	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	884-P
215-T	M	W	22	m	a	−	−	0	−	−	−	−	−	−	−	+	−	−	−	−	−	280-T
242-T	M	W	48	m	a	±	+	−	−	−	−	−	−	−	−	−	−	−	−	±	+	282-T

In table 2 are displayed the serological results in cases in which a recheck blood specimen and a review of the clinical status of the patient were deemed advisable.

DISCUSSION

Table 1 shows that, of the diagnostic methods, the Kolmer complement fixation and the Kahn standard precipitation test gave negative results with all sera from the adjusted group of tuberculous donors. The Eagle macroflocculation recorded one positive; the Eagle complement fixation, one positive and ten doubtful; the Kline diagnostic recorded four doubtful; and the Hinton, four positive and eight doubtful reactions.

Of the supersensitive procedures the Kahn presumptive recorded one positive and one doubtful reaction, and the Kline exclusion, five positive and eleven doubtful reactions. It should be recalled that these two methods are not advocated by their originators as diagnostic procedures.

The findings are capable of interpretation from two viewpoints. The first concerns the influence of tuberculous disease on the biological specificity of the tests, that is, the possibility that it introduces a factor or factors which alter the results by interfering with the characteristic interaction of the ingredients themselves. In expanding this view-point it is essential that this study be correlated with the contemporaneous 1938 Serodiagnostic Evaluation Study (8) in which the same group of serologists participated. In the latter study each of the test procedures returned completely negative reports in a group of control donors, the members of which were free from suspicion of syphilis and from evidence of other metabolic disturbances or manifest pathological conditions. With these findings serving as a basis, and taking into consideration the probable error of chance, it would seem that in only a few of the test procedures was an adverse effect of tuberculous toxaemia manifested. The greatest deviation is shown in the tests which, in accordance with the findings of the Evaluation Study, have been given the highest ratings in sensitivity. The Hinton rating in sensitivity is placed at 83.9 per cent and the Kline exclusion at 83.3 per cent. Although the Kline exclusion is not considered to be a diagnostic procedure, it serves here to illustrate that as the extremes of sensitivity are approached the possibility of interference by metabolic disturbance other than syphilis may tend to increase.

From the standpoint of tuberculosis serving as a factor which may interfere with accurate diagnosis of syphilis by serological methods, it

is necessary to consider the results obtained in the retesting of donors whose serum gave doubtful or positive reports in the original examination (table 2). One doubtful result or one doubtful and one positive result from test procedures may be disregarded. Chance error may account for these findings. Of the four doubtful reactions obtained by the Kline diagnostic test, all were recorded as negative upon reëxamination. Of the original findings with the Hinton test, five of the doubtful and three of the positive reactions were reversed to negative in recheck specimens. With the Kline exclusion test four doubtful and two positive reactions reversed to negative on the second examination. This test, however, recorded two positives on reëxamination which were doubtful with the original specimens and two doubtfuls which were

TABLE 3

Distribution of other than negative reports on sera from 450 nonsyphilitic tuberculous donors

DISTRIBUTION	SERA TESTED	PER CENT DOUBTFUL AND POSITIVE
Male	289	7.6
Female	161	8.1
Far advanced	293	7.5
Moderately advanced	155	8.4
Febrile	145	7.6
Afebrile	300	7.7

negative in the original sera. In clinical work the Eagle laboratory is guided in its interpretations of doubtful results in the complement fixation test by the findings in the macroflocculation procedure. It may be deduced from these reversals in the test results that, if the usual precautions are observed as regards rechecking in cases in which the syphilis status of the patient is clouded by the presence of a second infection, the possibility of an error in diagnosis is slight.

Emphasis should be placed on the fact that a minimum number of biological false-doubtful and false-positive reactions is shown in this study because each test procedure was in the hands of those most familiar with its performance and interpretation. In less experienced hands the degree of intereference and the possibility of diagnostic error would, in all probability, be increased.

Statistical treatment of the material as regards sex, stage of the disease,

and presence or absence of fever does not show significant findings (table 3).

CONCLUSION

Inasmuch as with the present serological tests for syphilis both typical and atypical false-doubtful and false-positive results are found in sera from tuberculous donors, it is evident that tuberculous toxaemia may contribute a confusing factor to syphilis serology. It should not, however, present a major problem in the clinical interpretation of results obtained with carefully conducted serodiagnostic procedures.

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REFERENCES

(1) Stokes, J. H.: Modern clinical syphilology, W. B. Saunders Company, 1935, p. 131.
(2) Dulaney, A. D.: Nonspecific cross-fixation of complement with the Wassermann and tuberculosis antigens, (Preliminary report), Amer. Rev. Tuberc., 1922, *6*, 192.
(3) Kilduffe, R. A., and Hersohn, W. W.: A note on the occurrence of positive Wassermann reaction and precipitation reactions in pulmonary tuberculosis, Ibid., 1929, *19*, 228.
(4) Stucky, G. C., and Huntley, W. B.: The Kahn test for syphilis in tuberculosis, Ibid., 1926, *14*, 724.
(5) Bowman, A. K.: Syphilis as a complication of tuberculosis, London Lancet, 1923, *205*, 1288.
(6) Horowitz, H. L.: An observation of syphilis and its treatment in patients admitted to a tuberculosis sanatorium, Illinois Med. Jour., 1927, *52*, 146.
(7) Snow, C. G., and Cooper, A. T.: Amer. Jour. Med. Sci., 1916, *152*, 185.
(8) Evaluation of Serodiagnostic Tests for Syphilis, 1938, (in print).

PULMONARY TUBERCULOSIS IN YOUNG ADULTS[1]

Particularly among Medical Students and Nurses

WILLARD B. SOPER[2] AND J. BURNS AMBERSON, JR.[3]

During the past ten or fifteen years there has been evolving a rather striking change in the concept of pulmonary tuberculosis in adults, especially in young adults.

It has long been taught that autopsy evidence adduced by Naegeli and Burkhardt, and others indicated a well-nigh universal infection with the tubercle bacillus; that tuberculin testing, beginning with Pirquet and widely employed for a period after 1907, confirmed the idea of general infection of city dwellers by the age of fifteen; that infection was acquired in early life (Behring) and that if the individual survived such infection he became allergic and was protected against ordinary or casual infection of the future; that those who developed the disease in adult life were infected from within (endogenously) by a mobilization of bacilli already in the body; that in some instances the protection conferred by an earlier infection was overwhelmed by subsequent exogenous infection. The more recently acquired knowledge alters this teaching to the extent that large numbers of individuals are now attaining adult life without having become infected with the tubercle bacillus.

Twenty years ago the value of the X-ray to discover minimal pulmonary lesions was not generally realized and the use of tuberculin for diagnosis was languishing except as employed by the pediatrician and the veterinarian. Then began a change of view. The Framingham Demonstration was launched in December, 1916. In 1924 Massachusetts inaugurated its ten-year plan to discover tuberculosis among school children by means of tuberculin and X-ray. In Oslo, Heimbeck began in 1924 his studies on nurses. Myers and different coworkers in Minnesota were beginning to glean results from the Lymanhurst School

[1] Presented before the Congress of American Physicians and Surgeons, Atlantic City, New Jersey, May 4, 1938.

[2] New Haven, Connecticut.

[3] New York City.

experience in Minneapolis. In 1928 Myers and Lees applied the tuberculin test to 2,093 freshmen entering the University of Minnesota. Rathbun was making intensive studies of high school students and doing much to stimulate interest. In a series of papers in 1930, Myers and his coworkers gave a summary of increasing numbers of tuberculin studies in the United States and abroad, most of them indicating a declining incidence of infection. The experience of Opie, Landis, McPhedran and Hetherington (1) in Philadelphia in their study of public school children, the results of which were published in 1929, was a notable exception. Interest in the problem of tuberculosis among school children was definitely under way.

Colleges and universities were slower in awaking. Ferguson (2) in October, 1937 published a history of the movement in them. The work at Minnesota under Myers and his coworkers was the most comprehensive and their tuberculin testing of entering students in 1928 was the greatest single step forward up to that time.

By 1930 an occasional college and university were groping along. A tuberculosis committee under the chairmanship of Doctor Ferguson was organized within the American Student Health Association at the first National Conference on College Hygiene at Syracuse in 1931. It recommended a program for tuberculosis case-finding which included tuberculin testing and X-ray examination. In the summer of 1931 there was held a preliminary conference, sponsored by the National Tuberculosis Association, to consider the whole problem of tuberculosis in college students and to work out a suitable program for its solution. Since then matters have moved rather rapidly. Tuberculosis surveys have been made in over two hundred American colleges and corresponding institutions. Not all have adequate regularly operated programs. Shepard, as a result of a detailed inquiry among American colleges during 1936 and 1937, reported that fifty had definite tuberculosis programs with regular annual examinations. The 1936–1937 report of the Tuberculosis Committee of the American Student Health Association utilized tuberculin testing figures from 85 institutions.

Long and Seibert (3) published a summary of results with tuberculin testing of college students. For the academic year 1935–1936 twenty colleges reported accurately completed tuberculin tests on 18,744 students, chiefly new entrants. Approximately two-thirds of the tests were of men and one-third of women. For New England and the Atlantic Coast the positives ranged from 46 to 48.9 per cent. For the

Middlewest the figures were distinctly lower, 20.6 per cent to 31 per cent. In New Mexico there were 71 to 80 per cent of positive reactors, presumably explained by the number of students from families having or having had tuberculosis. Northern California and Oregon were similar to the Atlantic Coast. Southern California was slightly higher with 50 to 60 per cent. Reports from colleges with large groups of men and women of approximately the same average age indicated that the frequency of positive tuberculin tests is somewhat higher in men than in women. Where the figures for academic freshmen were kept distinct from older entering students in graduate schools, the percentage of positives in the older group was higher by approximately 10 to 15 per cent.

The seventh annual report of the Tuberculosis Committee of the American Student Health Association for the academic year 1936–1937 bore upon 32,281 students the country over, all tested with the full strength of tuberculin when negative to a lesser strength. The percentage for the United States as a whole was 30.5. The figures generally were about the same as those of Long and Seibert of the previous year.

There is, then, fairly satisfactory knowledge as to the amount of tuberculous infection in entering college students over the country at the present time. From less common studies it is known that the percentage increases roughly 1 to 2 per cent per year during the college course and that the percentage of positives among men is approximately 5 per cent higher than among women.

As to the important question of the incidence and the significance of pulmonary disease among college and university students, one is on less certain ground. There is a lack of uniformity in the interpretation of roentgenograms, in the determination as between activity and nonactivity of the lesions found by X-ray, and in the methods of detection. The Tuberculosis Committee of the American Student Health Association (4) recommends, among other procedures, routine intracutaneous tuberculin testing of entering students and a single X-ray film of all positive reactors. They further recommend a yearly film of the positive reactors, a retesting every six months of all not reacting previously, and an X-ray film when reaction is found to have changed to positive. Needless to say, there are but few institutions where such a program can be fully carried out.

Only one set of figures, that of Stiehm (5) is included to illustrate the

findings of parenchymal lesions. Of 16,101 students tested with tuberculin at the University of Wisconsin from September, 1933 through February, 1938, 4,446 were positive. Of these positive reactors 4,215 were roentgenographed. Of the 4,215 roentgenographed, 188 showed parenchymal lesions. Of the 188 showing parenchymal lesions, 29 were regarded as active on enrolment and an additional 36 developed activity during their course of study. At Yale University, during seven years, parenchymal lesions were almost five times as numerous among the older entering students of the graduate schools as among the younger undergraduate freshmen. Race entered into the discrepancy as well as age.

The last American Student Health Association report gave interesting figures on the relative value of the old method of history and physical examination as compared with the newer method which adds the tuberculin test and the roentgenogram. In the year 1936–1937 there were 24 colleges and universities, with a total enrolment of 70,812, in which there were neither tuberculin testing nor X-ray studies. From these 24 institutions there were reported 20 cases of active pulmonary tuberculosis and 60 cases of clinically arrested disease. On the other hand, there were 13 institutions, with an enrolment of 20,758, employing X-ray. They reported 40 cases of active disease and 106 cases of clinically arrested disease. The latter institutions in which tuberculin and X-ray were employed, although having an enrolment less than one-third as large, reported twice as many cases of active disease and more than one and one-half times as many cases of clinically arrested disease. These figures support the accepted opinion that routine history and physical examination alone will fail to reveal many cases with lesions active or potentially so.

Along with studies of the incidence of infection in elementary school, high school and university students, there have been numerous studies in various other groups: in industry, CCC Camps, groups on relief, etc. While poor living conditions determine a higher incidence of tuberculous infection, the figures indicate that even in the less favored groups tuberculous infection is far from universal in young adult life. One cannot give a general figure for all but the qualifying factors are known. They include age, sex, race, economic condition, locality, occupation and known exposure to tuberculosis.

It is only relatively recently that the facts of lowered incidence of infection have been sufficiently appreciated as to affect the concept of

the pathology of tuberculosis in adults. Heimbeck and Scheel in Oslo, Myers and Opie in this country were among the first to direct attention to a new state of affairs. Allen Krause was suggesting it twelve years ago. A new generation has been and is entering high schools, colleges, universities, medical and nursing schools, and growing up outside these institutions, roughly one-half of whom have never been infected with the tubercle bacillus and, therefore, may be expected to react to the first tuberculous infection with so called primary infection types of disease, or what has been termed up to now, in this country, childhood type of infection.

As yet there have been but few satisfactory studies in the literature as to primary infection in adult life. Myers and his coworkers (6) in 1937 described and drew conclusions from 85 cases regarded as such. Their concluding paragraph stated the following which bears upon a later portion of this paper.

> In this student body of approximately 12,000 the number of students enrolled in the schools of nursing and medicine is a relatively small group, yet there is an overwhelming preponderance of lesions in this minor group, indicating to us that the problem of tuberculosis among young adults is most acute among those students who while in line of duty come in contact with tuberculous patients.

The subject of primary tuberculous infection in adults was one of three discussed at the last meeting of the International Congress on Tuberculosis held at Lisbon in September, 1937. The chief report was made by Scheel (7) of Oslo. It covered 229 cases, mostly women, from from various services of the Ulleval Hospital.

As to pulmonary lesions by X-ray, Scheel found them 67 times in the right lung field, 38 times in the left. In 77 instances they were small enough to be limited by a single rib or an intercostal space. The middle portion of the right lung in the vertical dimension was the seat of the greatest number of lesions, 29; the lower right lung field and middle left lung field were next with 13 in each. Hilum node reactions varied considerably and were less often gross in adults than in children.

"It is obvious," says Scheel, "that the great majority of primary infections run a benign course and cure themselves. Only thus can one explain the large number of individuals with positive tuberculin reaction in adult life who never develop clinical tuberculosis and who are unable to recall any period of illness which might be interpreted

as due to tuberculosis." However, Scheel recognizes the possibility of dissemination of primary infection by direct propagation such as to the pleura, and by metastases by the blood and lymph streams and bronchi. He recommends treating and observing the newly infected cases very closely since one cannot know their future resistance to the infection.

Badger and Spink (8) in their study of nurses described 7 cases which they regarded as having primary infection types of disease. Amberson and Riggins (9) found 6 presumably of this type in their study of nurses.

From what has gone before it seems evident that, as would be expected with only one-half or fewer of young adults infected with the tubercle bacillus, evidence of primary infection is being found among them. Differentiation between the primary form and the superinfection forms of disease is difficult. The primary form can be suspected when the individual has been so closely followed with the tuberculin test that only a short period has elapsed after the change to a positive reaction, and the roentgenogram shows a lesion in the lungs previously not present, and found on observation not to be due to some nontuberculous infection.

TUBERCULOSIS IN MEDICAL STUDENTS

The title of this paper was chosen on account of the interest of this assemblage in pulmonary tuberculosis not only in young adults generally but among medical students and nurses particularly. The old passive attitude toward the disease among them is outmoded. There has been an awakening of the public, and an increasing demand that hospitals and training schools assume responsibility for the protection of those given into their charge. Furthermore, the investment in each medical and nursing student is too great for disregard of any reasonable means to protect them against professional exposure and its results.

Numerous earlier reports indicated a greater incidence of tuberculosis among medical students than among the corresponding general population. In explanation, the emphasis was put upon the student's manner of living and upon his overwork, rather than upon his greater exposure to infection. With the newer methods of detection and with the improvement in the student's living conditions the emphasis is changing to degree of exposure.

Several of the leading medical schools have already inaugurated a program of prevention designed both to minimize exposure and to detect

an acquired lesion in its earliest stage by the use of tuberculin and X-ray. Most such programs are of recent adoption, too recent to draw conclusions. There have been, however, a few experiences of more recent date and from them one can obtain a fairly good idea of the present situation.

Hetherington, McPhedran, Landis and Opie (10) at the 1931 meeting of the Association of American Physicians caused a stir with their report on *Tuberculosis in Medical Students* at the University of Pennsylvania. In its final paragraph the report stated:

> The number of young adults with apical lesions of tuberculosis increases gradually with increasing age, but the incidence of these lesions in medical students, increasing rapidly in successive years of the medical course, with astonishingly high incidences in students of the fourth year, indicates that they are peculiarly subject to grave tuberculous infection.

Curiously, at the same meeting Fitz (11) stated that 484 students of the Harvard Medical School had been roentgenographed as part of a general physical examination and only one case of tuberculosis was detected.

In 1935 Hetherington, McPhedran, Landis and Opie (12) reported on a continuation of their work with the medical students of the University of Pennsylvania. The incidence of tuberculosis was still notably high.

Since 1935 most serious efforts have been made to reduce infection among the medical students of the University of Pennsylvania, and tuberculin and X-ray have been used freely for diagnosis. A report sent last March by Dr. H. B. Lees (13), in charge of the Student Health Service, would indicate that results are being obtained. In 1935–1936 there were 30 cases diagnosed tuberculosis by X-ray or otherwise, or 5.8 per cent of a total of 514 students; in 1936–1937, 19, or 3.9 per cent of a total of 481 students; in 1937–1938, 14, or 3.7 per cent of 379 students of the three upper classes. Of the 14 cases in the school this year, 12 are in the fourth year class. Doctor Lees hopes to start next year with almost a clean slate. In regard to tuberculin testing he states that during the last three years the medical students have shown about 70 per cent of positive reactions to tuberculin the first year and 97 or 98 per cent upon graduation.

In 1932 Herman, Baetjer and Doull (14) reported on tuberculosis among Johns Hopkins medical students. It was concluded then that

the evidence was insufficient to prove that medical students suffered a higher incidence of pulmonary tuberculosis than persons of similar age and economic status engaged in other occupations, but that such data as were available suggested that the student of medicine might be subjected to a higher risk.

On February 28, 1938, Doctor Herman (15) wrote that, since 1926, 1,132 students, including the class entering in the fall of 1937, have entered the Johns Hopkins School of Medicine. Of this number 16 have had outspoken pulmonary or pleural tuberculosis and one had tuberculosis of the urinary tract with no pulmonary lesion. In 2 the diagnosis of tuberculosis was very doubtful. Of the 16 students who developed tuberculosis, 2 had known tuberculous lesions prior to their admission to the school. The last case of active tuberculosis developing in a medical student at Hopkins was in March, 1935.

Doctor Herman wrote further that at the present time a routine X-ray film is taken of the lungs of all medical students on admission. They are urged to have yearly check-up films and about 60 per cent comply with the request. Routine tuberculin tests have not been made for several years but it is desired to reinstitute them.

Tuberculosis has not been a particularly major problem at the Yale School of Medicine. Among 427 students entering during eight years from 1930 through September, 1937, 6 cases were diagnosed by X-ray as having parenchymal lesions on admission. During the last five years the students have also been roentgenographed in the spring of their final year, 219 in all. Three showed minimal apical and one subapical disease. In addition, 2 of the 427 broke down during their course. Of the 12 students diagnosed, one was not permitted to continue beyond admission, 2 left the school for reasons other than health, 2 cured successfully during one year and have continued their work without trouble, 5 underwent no special treatment and have continued well, one is now under treatment and one is too recent for a statement. Six of the 12 might be regarded as having possibly contracted infection or superinfection during the medical course, although one of them had previously been exposed at home, another had a frank primary complex on admission and a third developed pleurisy with effusion in his second year.

Dr. Sarah Morris (16) has in operation a very comprehensive plan for the detection of tuberculosis at the Women's Medical College of Pennsylvania. Among other procedures all entrants are tested with

tuberculin and, when not reacting, every six months thereafter until positive. X-ray studies are made of all students each year and more often if desirable. They are also made of those changing from tuberculin-negative to tuberculin-positive during the year. Tuberculin testing in successive years has shown that 100 per cent react positively in the fourth year. On the other hand, the positive reactions on entrance from 1932 through 1937–1938 fell from a maximum of 63 per cent in 1933–1934 to a minimum of 32 per cent in 1937–1938. As to pulmonary findings, the 1937 survey showed in the school's enrolment of 107 students, one healed parenchymal lesion in the first year against 8 in the third and fourth years respectively. Of unstabilized lesions there was none in the first year but there were 4 in the fourth year. Of frank cases there was none in the first year against one in the third year and 2 in the fourth year. The last 3 cases were sent away for treatment.

At Columbia University (P. and S.), in addition to the complete history and physical examination, a single X-ray is taken of the lungs of all entering students. Late in the fourth year single films are again taken. Routine tuberculin tests have not been made but their desirability is being discussed. Doctor Flood (17) wrote that the medical students' record at the P. and S. for fifteen years, terminating two years ago, showed the incidence of recognized pulmonary tuberculosis to be only 0.4 per cent. A number of students known to have had clinical pulmonary tuberculosis before admission were not included. He remarks that the incidence of recognized active tuberculosis at the P. and S. is very considerably lower than that reported by some of the other medical schools.

From Harvard, Doctor Heath (18) wrote in February, 1938:

> We do a tuberculin test on each entering student and, if the test is negative, repeat it annually. An X-ray of the chest is also made of each entering student. If the tuberculin test is positive we repeat the X-ray annually. This system has been in force only one year. Previously, tuberculin tests and X-rays were done on the entire first and fourth year classes. About 60 per cent of first year students have positive tuberculins and about 85 per cent of fourth year students.
>
> I cannot say exactly what our incidence of pulmonary tuberculosis is. Last year we sent three students away to sanatoria, this year none (out of a student body of 500). In addition we have four students who have definite X-ray evidence of pulmonary lesions but without clinical signs who are under strict supervision. I should say that annually four cases of active or inactive

pulmonary tuberculosis are picked up. There is no doubt that tuberculosis is the most important organic medical problem in the medical school.

A letter was received last March from Doctor Barnett (19) of the Stanford University School of Medicine. The school in San Francisco has the students for the last two years; they are at Palo Alto up to then.

There were 420 students in San Francisco from the fall of 1933 when records were first kept. Four developed active pulmonary tuberculosis, a little less than 1 per cent. Six additional students showed X-ray evidence suggestive of active infection. Only one of these was put to bed. All recovered and have shown no further evidence of tuberculosis.

All students are examined physically and tested with tuberculin during the first year at Palo Alto. X-ray films are taken of all positive reactors and usually of most of the nonreactors. At the beginning of the third year and again at the end of the fourth year routine chest films are taken, and examination of the chest is repeated at the end of the fourth year. Tuberculin testing has not been repeated up to now after the first year, but this year routine annual tests are being started on all students negative to tuberculin the first year.

Doctor Stiehm (20) wrote last March of a rather remarkable experience at the University of Wisconsin.

Since 1933 there has occurred only one case of active tuberculosis among the medical students. The experience bears upon approximately 250 medical students who finished their medical training at Wisconsin and upon another 250 students who took only the first two years there. The students going through to graduation spend one week on the tuberculosis ward of the Wisconsin General Hospital, one week at a state sanatorium and one week at the Milwaukee County Sanatorium. During their tuberculosis experience they follow a strict isolation technique and wear masks and gowns when caring for the patients. All of their tuberculosis work is done during the senior year and, except for contact with general ward patients in the junior year, they have very little contact with the disease outside the fourth year.

In addition to the physical examination a tuberculin test is given on admission. Those having positive reactions have a single roentgenogram of the chest and are reëxamined during their student career at three- to eight-month intervals by fluoroscopy. Stiehm thinks that the medical students have very little opportunity for infection with

tuberculosis and that this fact probably explains the small incidence of the disease among them.

At the New York University College of Medicine, all entering students are tuberculin tested, and those students not reacting are retested at intervals until positive. Routine roentgenograms of the chest are made annually regardless of the tuberculin testing. Doctor Connor (21), who is in charge of the Health Service, reports that the incidence of tuberculosis in students has not thus far proved to be excessive.

In 1935 Scheel (22) of Oslo published the results of his study of medical students from 1926 to 1934. All of the 1,176 students underwent a period in the tuberculosis ward of the Ulleval Hospital and were tested by the Pirquet method, "often controlled by Mantoux." They were divided into groups, of which groups 1 and 2 are the most interesting. Group 1 comprised 361 students tuberculin-positive before the exposure in the tuberculosis ward; group 2, 207 students tuberculin-negative before or during exposure.

Like Heimbeck, Scheel finds there is a period of pre-allergy during the first six weeks of exposure and that the positive tuberculin tests due to exposure do not appear until after a lapse of about two months from the beginning. He finds that infection does not take place so rapidly in the medical students as among nurses, nor are the medical students infected with as much certainty.

By a statistical computation taking into consideration the period of exposure in the tuberculosis wards, group 1, with a positive Pirquet before exposure, showed an annual average morbidity of 1.47 per cent; group 2, with Pirquet negative at the beginning of exposure, showed an annual morbidity average of 4.31 per cent, almost three times as high.

As to the importance of superinfection in an individual previously infected and therefore reacting positively to tuberculin, Scheel reasons that, if superinfection often provokes new localizations of tuberculosis, there should be an increase of morbidity when the tuberculin-positive individuals continue exposed to new infection. He quotes Heimbeck's experience wherein one finds the following numbers of tuberculous affections among originally Pirquet negative nurses during the six years after exposure: 59, 20, 8, 1, 1, 4; the manifestations are found during the first two years and particularly in the first year. In the nurses with positive Pirquet reactions the corresponding figures are: 7, 8, 3, 2, 3, 1. Scheel had the same experience with his medical students. While the originally Pirquet negatives showed a morbidity of 6.5 per cent in the

first year and 3.9 per cent in the second, the originally Pirquet positives showed during the first years a variance but without increase.

To summarize the present situation as to medical students: they are, as a rule, less rapidly and less certainly infected than pupil nurses, but they still acquire infection to an excessive degree. The morbidity among them appears to vary. It seems alarmingly high in a few instances, but not in the majority of schools whose figures are known. Many of the leading schools have already instituted programs of prevention and case-finding. Where a definite program is lacking there is an increasing consciousness of the problem and effort to cope with it. The mortality seems not unduly high, probably because the cases developing are apt to be diagnosed and treated early.

It is interesting that figures compiled in 1930 by Miss Whitney (23), from ten representative states as to the mortality rate from respiratory system tuberculosis among all occupations of gainfully employed males, showed the rate for physicians and surgeons to be among the very lowest.

TUBERCULOSIS IN NURSES

Of recent years, tuberculosis among nurses has become a subject of considerable controversy. Danger of infection has been much emphasized; on the one hand that of primary infection, on the other that of superinfection.

Opinions are at variance; a few oppose admitting to the general hospital a pupil nurse negative to tuberculin lest she contract a primary infection and, through the acquired allergy, become a subject for superinfection disease; a few others oppose admitting a tuberculin-positive pupil lest, already allergic, she acquire superinfection disease. Both attitudes are based upon a profound fear of superinfection. The majority feel that neither attitude is either practical or grounded upon sufficient evidence. Many believe definitely that an existing stabilized infection confers a degree of protection.

At the outset it should be stated that the problem presents itself chiefly in the relatively young student nurse in the general hospital, who has an experience in tuberculosis as part of her training, or who, without such planned experience, may be exposed to unsuspected tuberculosis in general wards.

It is still the concensus that the older staff nurse in tuberculosis institutions does not develop disease materially more than the general

average of women of the same age. The most recent and careful study of this latter group was of 518 staff nurses at the Fitzsimons Hospital, by Pollock and Forsee (24). All were tuberculin-positive. Only 8, or 1.5 per cent, developed tuberculosis. These older nurses were apparently well protected against new exogenous infection.

Numerous articles have been published in the past, most of them going to show the incidence of pulmonary tuberculosis among nurses to be higher than among comparable groups of women generally. The best of the more recent literature was summarized by Miss Whitney (25) in 1935. Differing circumstances bearing upon the various studies make it impossible to draw a clear conclusion as to the relative incidence of disease. It seems unreasonable, indeed, to expect a uniformity of figures in view of the differences in age, locality, living conditions, exposure, methods of calculations, etc. Some of the more recent articles, however, do give some clue.

Ross (26), in 1930, reported a study of tuberculosis among nurses admitted to the Manitoba Sanatorium in that province. Among 800 nurses in training in the province 6 per cent broke down during their four year instruction, or 1.5 per cent per annum. The number of cases occurring among nurses was in excess of that among other women. Ross also states that a great majority of the nurses broke down in training or just afterward; that the incidence of tuberculosis is not unduly high among nurses after graduation; that it is highest in hospitals; that it appears to be particularly high among very young nurses.

Carmalt Jones (27), in 1933, reported an incidence of 3 per cent per annum during two years among a staff of 120 probationers, 25 staff nurses and 24 sisters in a New Zealand Hospital. All of the nurses did a three months' tour of duty at a tuberculosis sanatorium; all became Pirquet positive.

He compares the nurses' experience with that of 1,125 women of much the same age in three other schools not concerned with nursing. Among the latter there were only 2 cases of tuberculosis, one of them fatal. There were records of two deaths in ex-students from one school four years after graduation.

Mariette (28), in 1936, reported on an intensive study over a long period at the Glen Lake Sanatorium, Minnesota. He is a strong partisan of the idea of the protective influence of an existing infection. He accepts that there is a certain tuberculosis hazard in the nursing profession and urges all reasonable measures to meet it. He now

roentgenographs the nurses at three-month intervals to detect the earliest manifestations of disease.

In 1934 Geer (29) of St. Paul published the experience at the Ancker Hospital. From 1920 to 1928, 4.5 per cent of the nurses developed tuberculosis, three times the normal expected incidence. After 1928, all incoming nurses were tested with tuberculin and retested every six months. Roentgenograms were made on admission and subsequently with a change to a positive reaction. From September, 1928 to September, 1930, 5.5 per cent of the nurses developed tuberculous disease. An extremely rigid technique was introduced in the spring of 1931. Presumably as a result, only 1.6 per cent of nurses developed the disease from September, 1930 to the writing of the report in 1934, as against 5.5 per cent during the two years prior to the rigid technique.

In 1936 Amberson and Riggins (9) published a five-year study in tuberculosis among students in the Bellevue Hospital School of Nursing, New York City. The average age on admission was eighteen to twenty years. Of 539 candidates, 57.9 per cent were positive on admission either to 0.1 mg. of Old Tuberculin or to 1 mg. when negative to the smaller dose. About one-third of those failing to react to 0.1 mg. did react to 1 mg.

The originally tuberculin-negative nurses were retested every six months until reaction was noted. Of a group of 143 followed six months to three years, 37 became tuberculin-positive during the first year of training, 37 during the second and 10 during the third. Among 70 negatives followed for the full three years of the course all but 10 became positive. Thus it would seem that the majority of presumably uninfected nurses become infected sometime during their course which includes one month on a very busy tuberculosis service at the beginning of the second year of training. Here the nurses wear gowns when ministering to patients but face masks are not worn. Cleanliness and especially frequent washing of the hands are urged upon all nurses, but "contagion technique" is not employed.

During the five-year study 8 cases of tuberculosis came to light: 6 with pulmonary lesions, 1 with serofibrinous pleurisy and 1 of spondylitis. One case was diagnosed during the first year of training, 3 in the second and 4 in the third.

In September, 1937 Badger and Spink (8) reported a five-year study of student nurses in the Boston City Hospital, begun in January 1932. Thereafter, all nurses entering training underwent complete physical

examination, quantitative tuberculin tests and stereoscopic X-ray examinations of the lungs. Only those failing to react to 1 mg. of OT were declared negative and yearly tests were repeated of nonreactors. Stereoscopic X-ray examinations were repeated yearly on all student nurses, and oftener when indicated.

Of 470 nurses, 57.11 per cent were positive to tuberculin on admission. Of 126 nurses who finished their three year training and who were 66 per cent positive on admission, 90 per cent were positive on discharge.

There were 273 nurses, of whom 126 completed their course of training and 147 remained in training one year or more. Among the 273, 59.3 per cent were positive to tuberculin on admission. Eight tuberculous lesions were observed in this entire group. One case developed among the 162 initially positive reactors; 7 cases developed among the 111 initially tuberculin-negative.

From this limited experience the authors agree with Myers that the first infection type of tuberculosis is usually a benign form. However, a few small primary infections progress. Whether the lesion is benign or destructive cannot be determined at first, and all must be judged and followed with extreme care.

Stiehm wrote to us on March 1, 1938 that during the last five years there has not been a single case of active tuberculosis among 76 pupil nurses at the Wisconsin General Hospital at Madison. The same strict isolation technique is employed with them as with the medical students. They are required to work only eight hours per day and only four to six hours are spent on the wards. The nurses are closely followed by tuberculin and X-ray. The percentage of infection is increased by about 10 per cent during the three-year period of training. The known exposure is during a two-week period of training in the tuberculosis ward of the hospital.

The Yale School of Nursing has not suffered particularly from tuberculosis in recent years. Of 385 students roentgenographed on admission from September, 1930 through September, 1937, 6 were diagnosed as showing parenchymal lung lesions. Of the 6, three were sent away for treatment immediately or within a few months, 3 continued their work and remained well. Of 191 students again roentgenographed on graduation during the last five years, one showed a new minimal lesion for which she successfully underwent treatment, a second showed an apical lesion which has remained arrested during four years, a third quite recently showed a very small focus regarded

as arrested. One student developed pleurisy with effusion during her course and returned to work after one year of treatment. It should be stated that these pupils average about 23 years of age. They have experience in a tuberculosis ward and during three weeks in a tuberculosis hospital.

To Heimbeck (30) of Oslo is owed a debt for much of the present interest in tuberculosis among student nurses. His painstaking studies were begun in 1924 with modern methods. He has published a number of articles, the last that we have found being in summary form in December, 1936. The studies have been upon nurses entering and going through the Ulleval Hospital in Oslo where there is a large tuberculosis ward in which all pass a portion of their training period.

In starting his observations Heimbeck divided the nurses into two groups: group 1 comprised those who, on entering training, were "allergic, Pirquet positive, infected, without any symptoms of tuberculosis either in their earlier days or subsequently on investigation, who had passed through the stage of their primary infection without becoming ill." Group 2 comprised those who were "not infected at the time of entering training, Pirquet negative."

The groups were followed year after year. Some started in 1924, some in 1925 and so on, the latest in 1935. Every nurse was exposed to tuberculous infection and every one became infected within the first three years in the hospital.

An interesting finding was the difference in morbidity between those of the Pirquet positive on entering training and those Pirquet negative: 625 of the former with 2,659 observation years showed 27 instances of disease and no deaths; 280 of the latter with 561 observation years showed 96 instances of disease and 10 deaths.

Among the 27 instances of disease in the originally Pirquet positive group there were 8 of pleurisy, 4 of pulmonary tuberculosis with positive sputum, 7 with pulmonary inflammation with negative sputum, 7 of erythema nodosum. Among 96 instances of disease among the originally tuberculin-negative, there were 24 cases of pulmonary inflammation with negative sputum, 13 of pulmonary tuberculosis with positive sputum, 16 of pleurisy, 39 of erythema nodosum, 2 of meningitis and 2 of tuberculosis of the bronchial nodes.

In 1934 Myers, Diehl and Lees (31) presented a particularly strong appeal for the protection of nurses from infection by every possible means. They showed graphically how, in a school of nursing where

there was a tuberculosis service and no protection of any avail for the nursing students, the positive reactors increased from 30 to 35 per cent on entrance to over 95 per cent on graduation. In contrast, students entering the School of Education in the University of Minnesota where there was no exposure to tuberculosis showed only a 4 per cent increase between the first and graduating years.

To summarize as to nurses: although thoroughly satisfactory figures are not available to indicate the incidence of tuberculous disease among student nurses as against the similar age group of the general population of women, the prevailing opinion is strongly that such incidence is higher in the student nurse. Certainly this is the situation locally at times when it actually becomes necessary to appoint special committees to investigate.

Tuberculin studies almost without exception indicate an accretion of infection year by year quite out of proportion to the general population. This is found to be most marked where student nurses are in contact with known cases of tuberculosis as a part of their training. To a lesser degree it is found in hospitals where tuberculosis is not knowingly admitted.

The hazard is essentially to the young pupil nurse in the general hospital rather than to the older graduate.

To quote from Carmalt Jones (27):

> There appears to be an unduly high incidence of tuberculosis among young nurses. They come from sheltered families, at a period of life when according to clinical experience the incidence of pulmonary tuberculosis is high among women; . . . they are called upon to work unusually, though not unduly hard, and they are apt to tax their strength by indulgence in amusement which shortens their rest. In these circumstances they are brought into intimate contact with declared cases of tuberculosis and also with open and undeclared cases. It is the clear duty of hospital authorities to protect these women.

DISCUSSION

It seems clear that the earlier concept of universal infection with the tubercle bacillus by the age of fifteen years no longer holds for this country. There is to-day a generation of young adults of whom roughly a half or more are not allergic to tuberculin. A literally vast number of tuberculin tests supports the truth of this statement. On the other hand, one cannot prove that all individuals negative to tu-

berculin have escaped earlier infection, since there is evidence that skin hypersensitiveness may wane or disappear.

As to the tuberculin test, in this country most of the testing of young adults has been by the intracutaneous method of Mantoux. The earlier tests were performed with Old Tuberculin. More recently the Purified Protein Derivative (PPD) of Long and Seibert has been widely used. The differences in the results with the two are not sufficient to affect the conclusions drawn. In many instances the Mantoux recommendation of three tests, 0.01 mg., 0.1 mg. and finally 1 mg., has not been strictly followed. A two test method is often employed, the first with 0.01 mg. of OT or 0.1 mg., and the second or final test with 1 mg. of OT. With PPD, as generally recommended, the final dose is equivalent to 1 mg. of OT and the weaker or first dose is equivalent to $\frac{1}{250}$ of that strength. A considerable number of individuals require the full dose to bring out the reaction. Badger found that 19 per cent of 184 ultimately positive cases failed to react to 0.1 mg. but did react to 1 mg. Amberson found that about one-third of those who failed to react to 0.1 mg. did react to 1 mg. At Yale there has been a large experience with about 4,500 students of whom approximately 30 per cent of those finally positive did not react to the smaller dose of PPD but did react to the larger dose. It is generally accepted that 1 mg. of OT or its equivalent must be used intracutaneously to evoke the maximum number of positive tests. The Pirquet test is not equivalent to 1 mg. of OT intracutaneously. Figures as to the absence of allergy on the basis of tests with less than 1 mg. of potent tuberculin or its equivalent intracutaneously must be regarded as too high.

Is a negative tuberculin test a reliable index of absence of tuberculous infection? Generally speaking, it is so regarded although a few conditions, among them measles, influenza, miliary tuberculosis and terminal stages of pulmonary tuberculosis, may at times be accompanied by a temporary anergy. The reason is not clearly understood. These states would but rarely confuse the result in ordinary case-finding. Furthermore, and we believe that this fact has received too little attention, there is a not inconsiderable number of persons who, despite frank calcium deposits in the lungs or tracheobronchial nodes, fail to react to the full strength of tuberculin. In these instances the infection is assumed to be healed, or completely walled in. Whether such persons should be regarded as devoid of the protective effect of the earlier in-

fection is still a question. Howe (32) has shown that there may be a considerable daily fluctuation in skin sensitiveness to tuberculin.

Certain views have come to be generally accepted. One is that even the best history and physical examination will not reveal primary infection disease in adults any more than in children. Another view is that history and physical examination alone will miss very many cases of minimal superinfection disease. Boynton and her coworkers (33), among 126 cases of adult type pulmonary tuberculosis diagnosed by X-ray and clinical observation among University of Minnesota students from 1931–1935, found abnormal physical signs present in only 10 per cent of the fibrotic and minimal cases, and in only 23 per cent of the moderately advanced. Fellows (34), in 280 early cases of pulmonary tuberculosis diagnosed by X-ray, found abnormal physical signs in only 21 per cent. A third accepted view is that primary tuberculosis and also many cases of superinfection disease will not be accompanied by symptoms of severity sufficient to take the individual to the physician until the disease is in an advanced stage.

Incidentally, the last view goes far to explain why our sanatoria the country over admit about 5 cases of advanced disease to one of minimal. Until the X-ray, with or without tuberculin, is more generally employed by physicians this deplorable state will improve but little. It is our belief that, for the promotion of early diagnosis of tuberculosis, much emphasis should be put upon the education of the oncoming generation of physicians as to the particular importance of the X-ray as the only means by which, as a rule, the small lesion will be detected.

Bloch and his coworkers (35) in February, 1938 published a strong plea for the use of the X-ray for the detection of pulmonary tuberculosis, and indeed gave an exceptional summary of the present situation with regard to it and the significance of the findings for the whole tuberculosis problem.

The best present method to detect early pulmonary tuberculosis in the lungs of students appears to be that which employs both the tuberculin test and the roentgenogram in the beginning, and which then follows the positive reactors with roentgenograms, and the nonreactors with tuberculin until a change to positive takes place. Once the change has taken place the positive reactors too should be followed with roentgenograms.

Many studies, although not all, indicate that more tuberculosis

develops among those tuberculin-negative on exposure than among those tuberculin-positive, but the long-voiced fear lest primary infection in adult life play particular havoc seems not to be borne out. Primary infection in adults, other things being equal, appears to be distinctly less grave than in infants and no more grave than in older children. The great majority infected in young adulthood show no symptoms and no notable ill effects. However, the number in whom the effects are serious is apparently far from negligible. To what extent these later primary infections influence the high morbidity and mortality rate among young adults has not been definitely determined. Much is still to be learned in this regard.

The question enters as to whether an earlier infection manifested by definite allergy gives any protection from further exogenous infection. Where the number of observations is sufficiently large and sufficiently controlled there seems to be little argument. The Norwegians are convinced of this protective action and Heimbeck and Scheel are so certain of it that they vaccinate originally negative nurses and students with BCG and are not satisfied unless allergy is produced therewith. Indeed, Heimbeck's (36) last sentence in an article in 1933 was, "Tuberculosis-allergy is tuberculosis immunity, regardless of whether it is produced by tubercle bacilli or BCG."

Allen Krause has always maintained that allergy is accompanied by relative protection, and we personally agree. If one discards this concept he disregards a great mass of painstaking experimental work and a long series of attempts at active immunization of man and cattle. No one maintains that the protection conferred by an existing infection against exogenous infection is absolute. But one is justified in maintaining that relatively much protection is conferred, enough, in the opinion of many, to more than offset the harmful effects of allergy. However, the point seems relatively unimportant unless one acts upon his conviction to the extent of excluding either the allergic or the nonallergic student. What really is vital is the avoidance of infection.

Infection of nurses and medical students is presumably most often by aspiration. Scheel (7) cites the experiments of Chausse and of Lange to the effect that larger droplets adhere to the tracheal and bronchial mucosa and are expelled by the ciliated cells; that smaller droplets containing only one bacillus or a few units may be inspired into the lung alveoli. Slight infections would accord with relatively long periods before allergy develops and pathological changes become

manifest by X-ray. Is it not perhaps assumable that the positive tuberculin reactions acquired by medical students and nurses may be from very few bacilli in one institution and, therefore, accompanied by but little manifest disease; that in another institution more bacilli are offered, and to the degree of producing an alarming amount of disease? In both instances there might be a parallel increase in the number of positive reactors to tuberculin.

What can or should be done to reduce the infection in medical students and nurses to a minimum? Geer (29) instituted what is termed a strict medical aseptic technique to apply alike to all who come into contact with tuberculous patients: nurse, student, physician, personnel, visitor. Not only the usual gown is worn, but masks and caps. Details cannot be given here, but suffice it to say the technique goes far beyond any attempted previously. Stiehm at Wisconsin also carried out a rigid technique and Myers urges the utmost in precautions.

Institutions will go to differing lengths to prevent infection, but certain minimum measures should always be taken. There should be a contagion technique, at least to the point of wearing of special gowns and frequent washing of hands; methods of autopsy rooms and laboratories should be carefully scrutinized; every medical and nursing student, before beginning work with tuberculous patients, should be carefully instructed as to the hazards and as to the importance of technique, especially that of the patient's completely covering his mouth with sufficient layers of paper to retain expelled droplets (Jennings (37)); living and working conditions should be thoroughly healthful. In addition every effort should be made to discover tuberculosis in unsuspected cases admitted to the general hospital for conditions other than tuberculosis. The ideal plan to this end would be a roentgenogram of all cases on admission regardless of diagnosis, and routine examinations of sputum, whenever present, for tubercle bacilli. The unrecognized case of open tuberculosis in the general ward is a serious menace. The findings of a routine chest survey by X-ray of all patients entering the University of Michigan Hospital during eleven days are interesting in this and other regards (Hodges (38)).

Finally, there should be carried out a plan of tuberculin testing and roentgenographing every medical student and pupil nurse, in order that infection acquired will be detected at the earliest moment. There is no good medical school without at least one teacher vitally interested in pulmonary tuberculosis. The time and money required for tuberculin

testing and roentgenographing the relatively small number of students and pupil nurses are not great. They are small compared to the cost of one case out of control.

The treatment of pulmonary tuberculosis discovered among these students requires discrimination, judgment and experience on the part of the physician. Manifestly active cases should be put under treatment at once. In other instances, symptoms are vague or lacking, yet the small pulmonary infiltrations are potentially dangerous and should also be treated promptly and strictly. Only when the lesion is judged to be stable and fibrotic is it justifiable to postpone treatment pending a period of observation. In every case, observation should be at frequent intervals, at first with a roentgenogram every two to three weeks and close clinical study until the stability of the lesion is determined. Apparently stable lesions should be followed with roentgenograms for many years, at first every three months, and never less than once a year. As a part of the clinical study, examination of the fasting stomach contents, obtained in the morning by lavage, is to be recommended when the patient with a pulmonary infiltration reports that there is no sputum.

Probably the time is not far distant when public opinion will force the most thorough measures on hospital authorities. Already in certain states tuberculosis among hospital personnel is being debated as to its compensability.

There is another value to a case-finding program among students as great perhaps as that of prevention, namely the education of the student himself. As one personally and vitally concerned in the program of prevention, he absorbs two basic ideas that one wishes to inculcate: prevention and early diagnosis. Through the emphasis upon them as applied to him personally the student can scarcely fail to be impressed.

CONCLUSIONS

Tuberculous infection in young adults in this country and abroad is by no means universal. In this country at large, roughly speaking, 50 per cent of the white population under the age of twenty does not react to tuberculin. In some sections, as the Middlewest, the percentage of positive reactors is notably lower. A far-flung and increasingly effective effort is under way to detect early tuberculous infection and disease by the addition of the tuberculin test and the roentgenogram to the older methods.

The medical student and the pupil nurse are more exposed to tuber-

culous infection during their training than are those in other professions and occupations. This fact is attested by the disproportionate increase in positive reactions to tuberculin during their training. Infection in them may produce a primary type of lesion in the nonallergic individual or the superinfection type in the allergic. Studies strongly suggest that recognizable lesions occur more frequently in the nonallergic than in the allergic. Allergy may be said to be associated with a definite protective influence within certain limits.

The severity of infection of nurses and medical students appears to be decreasing owing to the greater application of methods to prevent exposure, improved diagnosis of the acquired disease in its earliest stage and elevated living standards. A greater and more widespread emphasis on prevention of infection and on early diagnosis, particularly by tuberculin and X-ray, should reduce the hazard of the student period to that of the general population, or even lower. With present knowledge the accomplishment of this reduction is not merely a possibility; it is a direct obligation upon institutions concerned.

REFERENCES

(1) Opie, E. L., Landis, H. R. M., McPhedran, F. M., and Hetherington, H. W.: Tuberculosis in public school children, Amer. Rev. Tuberc., 1929, *20*, 413.

(2) Ferguson, L. H.: A five year review of tuberculosis in college students, Ibid., 1937, *36*, 478.

(3) Long, E. R., and Seibert, F. B.: Tuberculous infection in American college students, Jour. Amer. Med. Assn., 1937, *108*, 1761.

(4) Proceedings of the Second National Conference on College Hygiene, 1936, p. 80, published by the National Tuberculosis Association, New York, 1937.

(5) Stiehm, R. H.: Personal communication. Material to be published.

(6) Myers, J. A., Diehl, H. S., Boynton, R. E., and Trach, B.: Development of tuberculosis in adult life, Arch. Int. Med., 1937, *59*, 1.

(7) Scheel, O.: Primo-infection tuberculeuse de l'adolescent et de l'adulte, Report of the Tenth Conference of the International Union against Tuberculosis, Lisbon, September, 1937, p. 213.

(8) Badger, T. L., and Spink, W. W.: First-infection type of tuberculosis in adults, New England Jour. Med., 1937, *217*, 424.

(9) Amberson, J. B., and Riggins, H. M.: Tuberculosis among student nurses, Ann. Int. Med., 1936, *10*, 156.

(10) Hetherington, H. W., McPhedran, F. M., Landis, H. R. M., and Opie, E. L.: Tuberculosis in medical students, Trans. Assn. American Physicians, 1931, *46*, 237.

(11) Fitz, R.: The problem of pulmonary tuberculosis in medical students, Ibid., 1931, *46*, 241.

(12) Hetherington, H. W., McPhedran, F. M., Landis, H. R. M., and Opie, E. L.: Further study of tuberculosis among medical and other university students, Arch. Int. Med., 1935, *55*, 709.

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REFERENCES

(1) Opie, E. L., Landis, H. R. M., McPhedran, F. M., and Hetherington, H. W.: Tuberculosis in public school children, Amer. Rev. Tuberc., 1929, *20*, 413.

(2) Ferguson, L. H.: A five year review of tuberculosis in college students, Ibid., 1937, *36*, 478.

(3) Long, E. R., and Seibert, F. B.: Tuberculous infection in American college students, Jour. Amer. Med. Assn., 1937, *108*, 1761.

(4) Proceedings of the Second National Conference on College Hygiene, 1936, p. 80, published by the National Tuberculosis Association, New York, 1937.

(5) Stiehm, R. H.: Personal communication. Material to be published.

(6) Myers, J. A., Diehl, H. S., Boynton, R. E., and Trach, B.: Development of tuberculosis in adult life, Arch. Int. Med., 1937, *59*, 1.

(7) Scheel, O.: Primo-infection tuberculeuse de l'adolescent et de l'adulte, Report of the Tenth Conference of the International Union against Tuberculosis, Lisbon, September, 1937, p. 213.

(8) Badger, T. L., and Spink, W. W.: First-infection type of tuberculosis in adults, New England Jour. Med., 1937, *217*, 424.

(9) Amberson, J. B., and Riggins, H. M.: Tuberculosis among student nurses, Ann. Int. Med., 1936, *10*, 156.

(10) Hetherington, H. W., McPhedran, F. M., Landis, H. R. M., and Opie, E. L.: Tuberculosis in medical students, Trans. Assn. American Physicians, 1931, *46*, 237.

(11) Fitz, R.: The problem of pulmonary tuberculosis in medical students, Ibid., 1931, *46*, 241.

(12) Hetherington, H. W., McPhedran, F. M., Landis, H. R. M., and Opie, E. L.: Further study of tuberculosis among medical and other university students, Arch. Int. Med., 1935, *55*, 709.

(13) LEES, H. D.: Personal communication.
(14) HERMAN, N. B., BAETJER, F. H., AND DOULL, J. A.: Tuberculous infection in medical students, Johns Hopkins Hosp. Bull., 1932, *51*, 41.
(15) HERMAN, N. B.: Personal communication.
(16) MORRIS, S. I.: Personal communication.
(17) FLOOD, C. A.: Personal communication.
(18) HEATH, C. W.: Personal communication.
(19) BARNETT, C. W.: Personal communication.
(20) STIEHM, R. H.: Personal communication.
(21) CONNOR, C. A. R.: Personal communication.
(22) SCHEEL, O.: La tuberculose parmi les étudiants en médicine à Oslo et sa prévention par la vaccination au B. C. G., Rev. de la tuberculose, 1935, *1*, 529.
(23) WHITNEY, J. S.: Death rates by occupation, published by the National Tuberculosis Association, New York, 1934.
(24) POLLOCK, W. C., AND FORSEE, J. H.: Reinfection among tuberculoallergic doctors and nurses at Fitzsimons Hospital, Amer. Rev. Tuberc., 1935, *31*, 203.
(25) WHITNEY, J. S.: Tuberculosis among nurses, A summary of the literature, Amer. Jour. Nursing, 1935, *35*, 1.
(26) ROSS, E. L.: Tuberculosis in nurses, Canad. Med. Assn. Jour., 1930, *22*, 347.
(27) JONES, D. W. C.: An inquiry into the incidence of tuberculosis among nurses in a New Zealand hospital, Tubercle, 1933, *15*, 59.
(28) MARIETTE, E. S.: The tuberculosis problem among nurses in a tuberculosis sanatorium, Ibid., 1936, *18*, 103.
(29) GEER, E. K.: Primary tuberculosis among nurses, Amer. Rev. Tuberc., 1934, *29*, 88.
(30) HEIMBECK, J.: Tuberculosis in hospital nurses, Tubercle, 1936, *18*, 97.
(31) MYERS, J. A., DIEHL, H. S., AND LEES, H. D.: The student nurse and tuberculosis, Jour. Amer. Med. Assn., 1934, *102*, 2086.
(32) HOWE, J. S.: Daily variations in the tuberculin reaction, Amer. Rev. Tuberc., 1938, *37*, 264.
(33) BOYNTON, R. E., DIEHL, H. S., AND SHEPARD, C. E.: The relative value of fluoroscopic, roentgenographic and physical examinations in a tuberculosis case-finding program in university students, Ibid., 1938, *37*, 49.
(34) FELLOWS, H. H.: Personal communication: from experience in diagnosis of tuberculosis among employees of Metropolitan Life Ins. Co., New York.
(35) BLOCH, R. G., FRANCIS, B. F., EISELE, C. W., AND MASON, E. W.: Roentgenological group examinations for pulmonary tuberculosis, Amer. Rev. Tuberc., 1938, *37*, 174.
(36) HEIMBECK, J.: Über Infektion und Vakzination bei Tuberkulose, Med. Klin., 1933, *29*, 1731.
(37) JENNINGS, F. L.: The permeability of paper sputum napkins, Amer. Rev. Tuberc., 1935, *32*, 304.
(38) HODGES, F. J.: The medical and economic advantages of roentgenographic chest survey of all hospital admissions, Ann. Int. Med., 1936, *9*, 1639.

COLLAPSE THERAPY IN PULMONARY TUBERCULOSIS[1,2]

A Follow-Up Study

HOWARD W. BOSWORTH AND C. RICHARD SMITH

Two recent publications have thrown some doubt on the value of collapse therapy in tuberculosis. Drolet (1) demonstrated that the ratio of deaths to new cases in the United States has remained the same during twenty years in spite of the increasing use of this form of treatment. Brand, *et al.* (2) in Reports to the Joint Tuberculosis Council of England compared the results in a large pneumothorax material from forty-two different institutions with those of two large control groups. Comparisons made on the basis of ratios of actual to expected deaths failed to show an advantage for the treated group.

On the other hand, there is a large number of publications of varying worth that support more or less enthusiastically the results of collapse therapy in tuberculosis. Excellent recent surveys of the literature have been made by Wilson (3), Rubin (4), Sinding-Larsen (5) and Hedblom (6). In 1935 the Committee on Artificial Pneumothorax of the American Sanatorium Association (7) reported the results of artificial pneumothorax in eighteen American institutions. Twenty-seven per cent of the cases were dead and three-fourths of the living were able to work. The Committee concluded that the value of the treatment was demonstrated. In a large number of collapse therapy cases analyzed by Sinding-Larsen (5), the ratio of actual to expected deaths was 12.1 as compared with a ratio of 22 for his controls. Hilleboe (8) reviewed the results in four large groups of patients treated during a period when little collapse therapy was used. He found ratios of actual to expected deaths to be approximately 4 for minimal cases, 16 for moderately advanced, and 40 for far advanced. However, his data for one institution showed ratios of 1.29, 5.48, and 16.98, respectively.

Two previous surveys on the results of treatment have been made at this institution. Barlow and Henning (9) reported on 1,600 patients

[1] Presented at a session of the Clinical Section at the 34th annual meeting of the National Tuberculosis Association, Los Angeles, California, June 22, 1938.

[2] From the Barlow Sanatorium, Los Angeles, California.

discharged between 1903 and 1921. There were 1,367 cases of pulmonary tuberculosis classified on admission: incipient, 2 per cent; moderately advanced, 65 per cent; and far advanced, 23 per cent. Eight per cent died in the institution. There were follow-up data on 1,090 cases, showing a 45 per cent mortality after discharge. Smith (10) reviewed 1,717 cases discharged between 1921 and 1935. There were 680 with destructive lesions and positive sputum on admission. These were grouped into two seven-year periods. In the first period, for 34 cases successfully treated with collapse therapy, there was a mortality of 41 per cent within 6 years; and for 345 cases not so treated, a mortality of 51 per cent. In the second period, of 219 collapsed cases,[3] 9 per cent died within six years, while 38 per cent of 82 untreated cases died. It is interesting that for the first seven years when collapse therapy was used in only 9 per cent of the patients, the mortality was 50 per cent; while for the second seven years when 71 per cent were collapsed the mortality was only 17 per cent.

It is not the intention in this paper to set up criteria for cases suitable for collapse therapy nor to prove that all advanced cases can be helped by these measures. By ascertaining the later results and the mortality in each of the methods reported, the effectiveness of collapse and the amount and type of treatment necessary, we hoped the study would show that this form of therapy when applied to selected cases offers not only to the more advanced types of pulmonary tuberculosis a better chance of recovery, but a reasonable chance of longevity when recovery has taken place.

To this end a study of all cases of pulmonary tuberculosis that have been discharged one year or more, and in which collapse therapy was primarily instituted at the Barlow Sanatorium, is presented. For the most part these patients come from the middle economic class. Cases are usually selected from the view-point of hopeful prognosis, and, in recent years, with collapse therapy in mind.

In collecting the data for this paper all living collapse therapy cases were contacted, and as far as possible the subsequent work was done by the Resident Staff at the Sanatorium. When this was not feasible in a few cases, X-ray, sputum and physical examinations from other sanatoria were included, or if this was impossible, X-ray films and sputum samples were sent by mail. The follow-up information was based on present

[3] Larger than the group reported here, since cases are included whose therapy was started elsewhere and continued in this institution.

history, including occupation and number of hours patient could work per day; X-ray (many of these being serial stereoscopic films from time of admission to last recheck examination); sputum studies by both concentration and culture, where necessary, in 82 per cent, and in the remainder either smear or concentration (usually three-day specimens); Mantoux tuberculin tests; and for future evaluation but not included in this paper, laboratory studies of blood counts, blood sedimentation, complement fixation and vital capacities.

All collapse cases have been reclassified according to the National Tuberculosis Association classification of 1930, admission rating being based on X-ray films in every instance. In the pneumothorax group, only those cases in which an air pocket had been established for six months were considered. Cases in which pneumothorax was started elsewhere were excluded due to insufficient preöperative information. Deaths occurring in the institution and within a year after discharge are included in the mortality data. Since this group comprises more than 43 per cent of the total deaths, it markedly increases our final mortality rate. After excluding those in which collapse had been established less than six months and those in which pneumothorax was started elsewhere, there were 197 cases.

Efficiency in securing follow-up data for each point of information was as follows: living or dead in 100 per cent; ability to work in 98 per cent; X-ray examinations in 91 per cent; sputum examinations in 91 per cent; physical examinations in 80 per cent. Tuberculin skin tests were given to 151, using for the most part the above cases. However, a few tests were made in the groups previously excluded from the tables to be used in this study.

Admission data revealed the following: total cases 197, or 100 per cent; far advanced 114, or 58 per cent; moderately advanced 83, or 42 per cent; cavitation shown by X-ray in 176, or 89 per cent; contralateral cavitation 15, or 7 per cent; sputum positive in 178, or 90 per cent; cavitation or positive sputum in 189, or 95 per cent.

The collapse methods employed are enumerated in table 1.

An idea of the periods of treatment may be gained from table 2. It will be noted that the average length of residence is unusually long. In later years the tendency has been to allow a shorter period of observation than is shown in the table—approximately six weeks to two months—before instituting collapse therapy, and a somewhat longer residence—around two years—in the sanatorium afterwards.

TABLE 1

Type of collapse therapy

Total cases	197
Artificial pneumothorax	162
Independent in	130
Combined with or supplemented by other procedures in	32
Phrenic (exairesis or crush)	50
Independent in	21
At termination of pneumothorax in	14
Combined with other procedures in	15
Thoracoplasty	32
Primary*	12
Secondary to other procedures	20

* Includes cases in which pneumothorax was attempted unsuccessfully.

TABLE 2

Periods of treatment in months

	AVERAGE	MINIMUM	MAXIMUM
Residence in sanatorium	19.8	2	72
Sanatorium care prior to collapse	4.4	−1	54
Duration of collapse	42.0	−1	150

TABLE 3

Final results—all cases

	NUMBER	PER CENT
Total cases	197	100.0
Dead	39	19.8
Living	158	80.2
Working full or part time	125	63.4
Negative sputum	114	57.8
Apparently cured	56	28.4
Arrested	51	25.0
Apparently arrested	3	1.5
Quiescent or active	38	19.2
Living but classification unknown	10	5.0

The crude results for the entire group are shown in table 3. It should be noted that 28.4 per cent are apparently cured, 25 per cent arrested, and 19.8 per cent dead.

In table 4 the present status of all cases is shown according to admission classification and years since discharge. Table 5 is a summary of the same material.

Table 6 gives the mortality data for all cases according to admission classification and years since discharge. The expected deaths were calculated from the U. S. Life Tables of 1929–1931 for males and females (11). Three of the deaths were due to causes other than tuberculosis. Almost half the deaths occurred in the institution or within the first year after discharge, and two-thirds of the deaths occurred within the first two years. Thus there is a progressive decrease in the mortality rate and the ratio of actual to expected deaths as the years since discharge increase.

In making an attempt to estimate the effectiveness of collapse, we used as criteria the closure of cavity as demonstrated by serial X-ray films and the disappearance of tubercle bacilli from the sputum. On this basis, collapse was effective in 63 per cent of the cases. The final results according to the type of collapse are shown in table 7. We are not satisfied that negative sputum reports were anywhere near dependable until the last few years, when concentration and cultures were added to the smear method. This may account for the poor results in the lower half of the so called effective collapse column. Using the above criteria also necessitated exclusion of several cases which had neither demonstrable cavity nor positive sputum on admission. In spite of the few unsuccessful cases where collapse was effective and those successful ones where collapse was ineffective, the general shift in both columns shows the necessity for effective collapse and indicates the need for further procedures when this is not accomplished.

Although table 8 shows a higher percentage of unsatisfactory results for patients with cavities 4 cm. or larger or with bilateral cavitation, it is quite encouraging to note that the proportion of apparently cured and arrested cases is sufficiently high to justify collapse procedures.

Artificial pneumothorax was used in 162 cases. In 130 this treatment was independent, being supplemented in some by pneumonolysis and occasionally by phrenic paralysis at the time of reëxpansion. In 32 cases additonal collapse therapy became necessary. To be considered first is the group of independent pneumothoraces. Of the total of 130, 79 have been reëxpanded, 68 per cent of these from two to nineteen years. The crude final results appear in table 9, showing 34.6 per cent apparently cured, 28.4 per cent arrested, and 19.2 per cent dead.

TABLE 4

Entire group—present status according to years since discharge

YEARS SINCE DISCHARGE	ALL CASES			APPARENTLY CURED			ARRESTED			APPARENTLY ARRESTED, QUIESCENT OR ACTIVE			LIVING, CLASSIFICATION UNKNOWN			DEAD		
	M. A.	F. A.	Total	M. A.	F. A.	Total	M. A.	F. A.	Total	M. A.	F. A.	Total	M. A.	F. A.	Total	M. A.	F. A.	Total
1–2	20	17	37	1		1	16	5	21		9	9				3	3	6
2–3	13	10	23	4	2	6	3	4	7	3	2	5				3	2	5
3–4	11	12	23	2	1	3	4	3	7	3	6	9	1	1	2	1	1	2
4–5	14	11	25	5	3	8	7	1	8	1	6	7		1	1	1		1
5–6	7	18	25	3	8	11	2	1	3		5	5		1	1	2	3	5
6–7	4	13	17	3	6	9	1	3	4		3	3					1	1
7–8	4	4	8	2		2					1	1	2		2		3	3
8–9	1	3	4	1	1	2		1	1		1	1						
9–10	2	5	7	2	3	5					1	1		1	1			
10–11	1	2	3	1	1	2											1	1
11–12	2	2	4										1		1	1	2	3
12–13	2	4	6		2	2								1	1	2	1	3
13–14		2	2		1	1											1	1
14–15		5	5														5	5
15–16	2	5	7	2	2	4								1	1		2	2
16–17		1	1														1	1
Total....	83	114	197	26	30	56	33	18	51	7	34	41	4	6	10	13	26	39

The present status of this group according to years since discharge is shown in table 10. Table 11 is a summary of this material.

TABLE 5

Entire group—present status according to years since discharge—summary

YEARS SINCE DISCHARGE	TOTAL CASES	APPARENTLY CURED OR ARRESTED		APPARENTLY ARRESTED, QUIESCENT OR ACTIVE		LIVING, CLASSIFICATION UNKNOWN		DEAD	
		Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent
1–2	37	22	59.5	9	24.3			6	16.2
2–5	71	39	54.9	21	29.6	3	4.2	8	11.3
5–17	89	46	51.7	11	12.3	7	7.9	25	28.1
Total.....	197	107	54.3	41	20.8	10	5.1	39	19.8

TABLE 6

Mortality data for the entire group

YEARS SINCE DISCHARGE	EXPOSED TO RISK			ACTUAL DEATHS			EXPECTED DEATHS			MORTALITY RATE PER CENT			RATIO ACTUAL TO EXPECTED DEATHS		
	M. A.	F. A.	Total	M. A.	F. A.	Total	M. A.	F. A.	Total	M. A.	F. A.	Total	M. A.	F. A.	Total
0–1	83	114	197	7	10	17*	.32	.43	.75	8.4	8.8	8.6	21.8	23.0	22.5
1–2	76	104	180	5	6	11†	.26	.41	.68	6.6	5.8	6.1	19.2	14.5	16.2
2–5	134	228	362	1	7	8	.50	.86	1.36	.7	3.1	2.2	2.0	8.1	5.9
5–16	76	159	235		3	3	.25	.70	.95		1.9	1.3		4.2	3.1
Total....	369	605	974	13	26	39	1.34	2.41	3.75	3.5	4.3	4.0	9.7	10.8	10.4

* Two deaths due to causes other than tuberculosis.

† One death due to causes other than tuberculosis.

TABLE 7

Effectiveness of collapse—cavity closed and sputum negative

FINAL RESULT	COLLAPSE EFFECTIVE	COLLAPSE INEFFECTIVE
	per cent	*per cent*
Apparently cured	42	7
Arrested	34	10
Apparently arrested	1	1
Quiescent	9	21
Active	3	11
Living but classification unknown	5	6
Dead	6	44
Total	100	100

Table 12 gives the mortality data according to the number of years after discharge. Three deaths were due to causes other than tuberculosis.

In the group of 79 expanded pneumothoraces there are 45 apparently cured, 10 arrested, and 12 dead. That it not be thought the independent pneumothorax group is too selected, figures for the 32 combined cases are also given. In these, the death rate of 18.7 per cent approximates the above, and the apparently cured and arrested account for 40.6 per

TABLE 8

Cavities and final results

FINAL RESULT	CASES WITH CAVITIES 4 CM. OR MORE	CASES WITH BILATERAL CAVITATION
	per cent	*per cent*
Apparently cured	13	33
Arrested	13	7
Apparently arrested	2	
Quiescent	13	7
Active	15	
Living but classification unknown	7	
Dead	37	53
Total	100	100

TABLE 9

Artificial pneumothorax, independent

	NUMBER	PER CENT
Total cases	130	100.0
Moderately advanced	62	47.7
Far advanced	68	52.3
Dead	25	19.2
Living	105	80.7
Working full or part time	92	70.7
Negative sputum	84	64.6
Apparently cured	45	34.6
Arrested	37	28.4
Apparently arrested	1	.7
Quiescent or active	12	9.1
Living but classification unknown	10	7.6

cent which, considering the more complicated therapy, compares very favorably.

Phrenic nerve paralysis, either temporary or permanent, was employed in 50 cases, 40 here, and 10 after discharge. It was used as an independent measure in 21, as an aid to lung reëxpansion in 14, and combined

with other procedures to effect collapse in 15 cases. The final results for independent phrenicoexairesis are given in table 13. In justice to this method which was used more frequently as a combined measure or

TABLE 10

Independent pneumothorax—present status according to years since discharge

YEARS SINCE DISCHARGE	TOTAL CASES	APPARENTLY CURED	ARRESTED	APPARENTLY ARRESTED, QUIESCENT OR ACTIVE	LIVING, CLASSIFICATION UNKNOWN	DEAD
1–2	21		15	3		3
2–3	17	6	5	3		3
3–4	13	1	7	2	2	1
4–5	16	7	5	2	1	1
5–6	15	8	2	1	1	3
6–7	13	9	3	1		
7–8	7	2		1	2	2
8–9	1	1				
9–10	5	4			1	
10–11	2	1				1
11–12	1				1	
12–13	5	1			1	3
13–14	2	1				1
14–15	5					5
15–16	6	4			1	1
16–17	1					1
Total.....	130	45	37	13	10	25

TABLE 11

Independent pneumothorax—present status according to years since discharge—summary

YEARS SINCE DISCHARGE	TOTAL CASES	APPARENTLY CURED OR ARRESTED		APPARENTLY ARRESTED, QUIESCENT OR ACTIVE		LIVING, CLASSIFICATION UNKNOWN		DEAD	
		Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent
1–2	21	15	71.4	3	14.3			3	14.3
2–5	46	31	67.4	7	15.2	3	6.6	5	10.8
5–17	63	36	57.1	3	4.8	7	11.1	17	27.0
Total.....	130	82	63.1	13	10.0	10	7.7	25	19.2

on termination of pneumothorax, we should state that we have not considered it the collapse method of choice for cavity closure if pneumothorax could be established. For that reason many of our phrenic operations have been performed only after we were unsuccessful in

establishing a pneumothorax pocket. Naturally, the amount of rise of the diaphragm was in some cases disappointing. The series, therefore, is too small to mean much on critical analysis. It is sufficient to point out that 28.5 per cent are apparently cured or arrested, our lowest group; 42.8 per cent are only quiescent or active; and 19 per cent are dead.

Thoracoplasty was performed in 32 cases, 9 of which were operated upon elsewhere. These are classified as primary 12, secondary to pneumothorax 17, and secondary to phrenic paralysis 3. The results are shown in table 14. Again, this number is small, only 32 being presented, but when it is considered that 24, or 75 per cent, were far advanced, the final results of 40.6 per cent apparently cured or arrested appears to more than justify the procedure.

As a means of determining the proper time for discontinuing pneumothorax, Neal (12) proposed the tuberculin skin test, the lung being allowed to expand when the patient was negative to 10 mg. of OT. We have made Mantoux tests on 151 patients a few months to seventeen years after collapse therapy was instituted. Both OT and PPD were used in the majority and one or the other in all. Fresh dilutions of OT (Cutter) were made weekly. PPD dilutions were made the same day. Reactions were read according to the criteria of Aronson in the American Review of Tuberculosis Supplement, December, 1934.

Of the 151 cases tested, 149 reacted positively, all but 2 to a maximum dose of .01 mg. OT or first strength PPD. Of the two cases with negative reactions, one was negative to first strength PPD and the other to a tenth of this dosage, further tests being refused. It should be pointed out that in this group were a number of persons whose lungs have been expanded many years. Among those tested were 54 apparently cured cases and 50 arrested.

It is our impression that the literature concerning the disappearance of râles in healed tuberculosis has been somewhat misleading. Particularly is this so in the cases in which collapse therapy has been employed. Riviere (13), Clifford (14), Bruns (15), and Amberson (16) have been among the few who have commented upon the persistence of râles in healed tuberculosis, and all have given plausible causes for their existence. It is not within the province of this paper to state whether they are due to residual changes, bronchiectasis, or emphysema, but we have found that in 40 out of 50 apparently cured cases the persistence of moist râles was noted on physical examination of the chest.

TABLE 12

Mortality data for independent pneumothorax cases

YEARS SINCE DISCHARGE	EXPOSED TO RISK			DEATHS			MORTALITY RATE PER CENT		
	M. A.	F. A.	Total	M. A.	F. A.	Total	M. A.	F. A.	Total
0–1	62	68	130	5	8*	13	8.0	11.8	10.0
1–2	57	60	117	3	4†	7	5.3	6.7	5.9
2–5	104	138	242		2	2		1.5	.8
5–16	64	121	185		3	3		2.5	1.6
Total.....	287	387	674	8	17	25	2.8	4.4	3.7

* Two deaths due to causes other than tuberculosis.

† One death due to causes other than tuberculosis.

TABLE 13

Phrenicoexairesis, independent—final results

	NUMBER	PER CENT
Total cases.....	21	100.0
Moderately advanced.....	8	38.0
Far advanced.....	13	61.9
Dead.....	4	19.0
Living.....	17	80.9
Working full or part time.....	11	52.3
Negative sputum.....	8	38.0
Apparently cured.....	4	19.0
Arrested.....	2	9.5
Apparently arrested.....	1	4.7
Quiescent or active.....	9	42.8
Living, classification unknown.....	1	4.7

TABLE 14

Thoracoplasty, primary and secondary—final results

	NUMBER	PER CENT
Total cases.....	32	100.0
Moderately advanced.....	8	25.0
Far advanced.....	24	75.0
Dead.....	9	28.1
Living.....	23	71.9
Working full or part time.....	14	43.7
Sputum negative.....	14	43.7
Apparently cured.....	5	15.6
Arrested.....	8	25.0
Apparently arrested.....	1	3.1
Quiescent or active.....	9	28.1

DISCUSSION

Although the mortality of 19.8 per cent in this group is not strictly comparable with that of 45 per cent, 52 per cent and 38 per cent, respectively, in the noncollapse groups reported from this institution (10, 11), we feel the difference is certainly in favor of collapse therapy. The final ratios of 9.7 for moderately advanced cases and 10.8 for far advanced cases may be compared with the ratios of 16 and 40, respectively, estimated by Hilleboe (9).

While pneumothorax, our treatment of choice, shows the better long time results, the proportion of arrested and apparently cured cases for other types of collapse therapy has been most gratifying.

We should like to emphasize particularly the absolute numbers of apparently cured cases. These patients have been subjected to rigid examinations; they are well and have remained well for years. We firmly believe pulmonary tuberculosis is a curable disease and that persons once cured remain so permanently.

In our series of tuberculin tests the sensitivity to tuberculin did not disappear following collapse therapy. We, therefore, feel that the use of this measure as a criterion for expansion is dangerous.

Since moist râles may be found frequently in cases of tuberculosis healed by collapse therapy, we believe this sign as a criterion of activity should be used with caution.

SUMMARY

1. In 197 cases the mortality is 19.8 per cent; the mortality rate on the basis of person-years is 4.0 per cent; the ratio of actual to expected deaths is 10.4; 54 per cent are arrested or apparently cured.

2. Pneumothorax has resulted in arrest or apparent cure in 63 per cent, phrenic paralysis in 28 per cent, thoracoplasty in 40 per cent.

3. Cavities 4 cm. or more in diameter, or bilaterally located, are least amenable.

4. Collapse of the involved portion is essential; and if not accomplished by one procedure, a further program is indicated.

5. In our experience, the sensitivity to tuberculin does not disappear following collapse therapy.

6. Moist râles persist in the majority of apparently cured cases.

Appreciation is expressed to Dr. Emil Bogen for suggestions in regard to arrangement of some of the tables.

REFERENCES

(1) DROLET, G. J.: Present trend of case fatality rates in tuberculosis, Amer. Rev. Tuberc., 1938, *37*, 125.

(2) BRAND, W., *et al.*: The results of artificial pneumothorax treatment, Reports to the Joint Tuberculosis Council, Tubercle Supplement, February, 1937.

(3) WILSON, J. L.: The results of collapse therapy in pulmonary tuberculosis, New England Jour. Med., 1937, *217*, 432.

(4) RUBIN, E. H.: Pneumothorax treatment of pulmonary tuberculosis, Medicine, 1937, *16*, 351.

(5) SINDING-LARSEN: On the collapse treatment of pulmonary tuberculosis, Acta Med. Scandinav., Supplement 80, 1937.

(6) HEDBLOM, C. A.: The results of extra-pleural thoracoplasty in the treatment of pulmonary tuberculosis, Jour. Thoracic Surg., 1934, *4*, 55.

(7) PETERS, A., POPE, A. S., MORRISS, W. H., PACKARD, E. N., AND MILLER, O. O.: A survey of artificial pneumothorax in representative American tuberculosis sanatoria, 1915–1930, Amer. Rev. Tuberc., 1935, *31*, 85.

(8) HILLEBOE, H. E.: The comparative mortality of patients discharged from tuberculosis sanatoria, Ibid., 1936, *34*, 713.

(9) BARLOW, W. J., AND HENNING, O. F.: Results of twenty years of sanatorium treatment, Tr. 19th Ann. Meeting Natl. Tuberc. Assn., 1923, p. 203.

(10) SMITH, M.: The treatment of cavities including their disappearance and recurrence, Tr. 31st Ann. Meeting Natl. Tuberc. Assn., 1935, p. 394.

(11) DUBLIN, L. I., AND LOTKA, A. J.: Length of life, The Ronald Press Co., New York, 1936.

(12) NEAL, J. R.: Allergy as a guide in terminating artificial pneumothorax, Amer. Rev. Tuberc., 1935, *32*, 326.

(13) RIVIERE, C.: Damaged lungs and bronchiectasis, British Med. Jour., January, 1923, p. 141.

(14) CLIFFORD, R.: Interpretation of apical râles in pulmonary tuberculosis, New England Jour. Med., 1928, *198*, 948.

(15) BRUNS, E. H.: Parenchymal râles in tuberculosis, Jour. Amer. Med. Assn., 1925, *85*, 739.

(16) AMBERSON, J. B.: The process of resolution in pulmonary tuberculosis, Amer. Rev. Tuberc., 1936, *33*, 269.

TUBERCULOUS TRACHEOBRONCHITIS[1,2]

J. LAWRENCE H. HAWKINS, JR.

Within the past few years there has been an increasing interest in tuberculous tracheobronchitis. In recent literature there have been numbers of articles to call our attention to its frequent occurrence and its importance. Most of these articles impress me as being the result of careful observations and thoughtful analysis. The stenotic stage of tuberculous tracheobronchitis has had extensive description by Eloesser (1). By calling to our attention the severity of ulcerative tuberculous tracheobronchitis Samson (2) was successful in stimulating a deserving interest in the study of early lesions. More recently Tuttle (3) and Myerson (4) have shown that there are many tuberculous tracheobronchial lesions of less severity which usually heal either with or without treatment.

Bronchoscopy, as perfected by Chevalier Jackson (5) and others, has been the most valuable aid in recognizing tuberculous tracheobronchitis. Only a few years ago tuberculosis was considered a contraindication to bronchoscopy. This opinion is now obsolete. A recent article by Clerf (6) on peroral endoscopy devotes more space to bronchoscopy in tuberculosis than in any other condition. In the past two and one-half years there has been a marked increase in the number of patients bronchoscoped at Olive View Sanatorium.

The pathology of tuberculous tracheobronchitis was described more than a century ago by Louis (7). He found more lesions in the trachea than in the bronchi, but tells us that he searched more carefully in the trachea than in the bronchi. Powell (8) in 1893 described tuberculous ulcers in the bronchi which healed by fibrosis causing stenosis. Cornet (9) in 1904 classified the lesions of tuberculous tracheobronchitis as we recognize them to-day. He believed they began as submucosal nodules in the bronchi which either became caseous and ulcerated, or produced stenosis. In 1901 at the museum of the British Congress on Tubercu-

[1] Presented at a session of the Clinical Section at the 34th annual meeting of the National Tuberculosis Association, Los Angeles, California, June 22, 1938.

[2] From the Olive View Sanatorium, Olive View, California.

losis (10) there were nine pathological specimens showing ulcerations and submucosal tubercles in the tracheobronchial tree.

More recently there has been extensive work by Reichle and Frost (11), Burgher, Littig and Culp (12), and others, especially as to the pathogenesis of tuberculous tracheobronchitis. We have nothing to add to their observations. Most of the lesions we have seen are on the posterolateral walls of the bronchi and trachea. Most of them seem to develop submucosally. Most of them, but not all, seem to begin in the smaller bronchi, extend to the larger bronchi and finally to the trachea. Twenty-two per cent of our patients with tuberculous tracheobronchitis also had tuberculous laryngitis; but 50 per cent of the patients with tuberculous laryngitis whom we have bronchoscoped also have a tuberculous tracheobronchitis. The types of tuberculous tracheobronchitis we recognize bronchoscopically concur with those described by Samson (2) and others: (A) diffuse and nodular submucosal; (B) ulcerative; (C) fibrostenotic; and various combinations of these. They each appear to be different stages in the same process. The severity of lesions varies widely in different patients. The degree of acuteness and chronicity varies widely in each stage.

I wish to report the results of bronchoscopy in 516 patients at Olive View Sanatorium; 132 of these patients showed gross evidence bronchoscopically of tuberculous tracheobronchitis. In most of these the involvement was unilateral. In 43 of these patients there was extensive ulceration of a major bronchus; with extension into the trachea in 27 of them. In a few, a main bronchus was completely obliterated. When the bronchoscope could be inserted down the ulcerated stem bronchus, the ulceration was usually seen to extend from the upper lobe bronchus of that side. The ulcerated areas were usually covered with granulations varying from fine pinpoint granules to heavy papillae. In some the granulations were fiery red and bled easily, some were a dull rust color, and in others the granules were pale, as if water-logged. In 33 there was a marked stenosis of a major bronchus, without extensive ulceration. In the remaining 59 patients there was a smaller amount of tracheobronchitis, chiefly ulcerative or fibrostenotic, of a stem bronchus. Submucosal nodules, when present, varied in size from minute to 3 or 4 mm. in diameter, and were covered with a rough thickened mucosa.

The high percentage of tuberculous tracheobronchitis we find in the patients bronchoscoped at Olive View Sanatorium, I attribute to the

painstaking work of our clinicians, roentgenologist and medical director in selecting patients for bronchoscopy. Our opinion at present is that bronchoscopy is not advisable in all patients with pulmonary tuberculosis. If they will accept it, and are not too ill, we bronchoscope all patients who have the classical symptoms and signs of tuberculous tracheobronchitis: asthmatoid attacks; oral wheeze; rhonchi; dyspnoea out of proportion to vital capacity; excessive cough with tenacious sputum; constant tendency to throat clearing, nonproductive; persistently positive sputum with no other evidence of pulmonary tuberculosis. Samson and his coworkers (2) have elaborated on these symptoms in great detail.

Direct or indirect roentgenological evidence most often prompts us to bronchoscope patients: a narrowed trachea or bronchus, shown either with or without opaque oil; thickened bronchial walls; atelectasis; cavities which increase in size with pneumothorax, or which do not close with an otherwise successful pneumothorax; cavities with a fluid level; large, round, thin-walled cavities; cavities with extensive perifocal reaction; hilar cavities; cavities which appear and disappear, or become larger and smaller from time to time; areas of infiltration which appear and disappear; bronchogenic spread without a visible cavity.

Sometimes at thoracoscopy cavities can be seen to "balloon" on inspiration, and feel like a tennis ball on expiration, because of incomplete emptying. Where there are signs of a bronchial check-valve, patients should be bronchoscoped to see whether their tuberculous tracheobronchitis has extended into a bronchus large enough to be amenable to treatment.

Patients scheduled for major thoracic surgery should be routinely bronchoscoped. If they have an active ulcerative tuberculous tracheobronchitis it should be treated before surgery. If there is a rapidly progressing tuberculous tracheobronchitis, especially on the contralateral side, surgery is contraindicated. If there is a stenosed bronchus the thoracic surgeon will want to know its location. The stenosis may need to be dilated before surgery, or retained secretions aspirated from below it after surgery.

Since most of our cases of tuberculous tracheobronchitis have been followed for an average of only about one year it would be premature for me to say that the prognosis is less grave than frequently reported. However, the opinion we have formed is that this is so. Seventeen patients of our series, at first bronchoscopy, had what appeared to be an

entirely healed fibrostenotic tuberculous tracheobronchitis. Some of these gave a history of symptoms of ulcerative tuberculous tracheobronchitis several years previously, or had serial roentgenograms suggestive of tuberculous tracheobronchitis for several years. A high percentage of our patients with tuberculous tracheobronchitis have made definite improvement in their pulmonary tuberculosis during the time they have been observed. Of those who have had repeated bronchoscopic examinations, many have shown improvement in their tracheobronchial lesions, either with or without local treatment. While only seven of our patients with a bronchoscopic diagnosis of tuberculous tracheobronchitis have died, a few patients who have died at Olive View Sanatorium during this period had symptoms of tuberculous tracheobronchitis but were too sick for bronchoscopy. In general, the prognosis depends on the extent of the tracheobronchitis, the pulmonary involvement and the general condition of the patient.

The following three case reports of apparently healed tuberculous tracheobronchitis are typical of several we have observed.

E. S.: No. 9295, a divorced white female, aged 34, was first admitted to Olive View Sanatorium September 3, 1930. Her onset was pleuritic three months before. Roentgenographic study showed infiltration in both upper lobes fairly discrete, with multiple cavitation in the right upper lobe and one small cavity in the left upper lobe. On November 17, 1931 she had a cystic left ovary removed because of pelvic distress. Her pulmonary progress was satisfactory, cavities closed and infiltration fibrosed. In January, 1932 she began having asthmatoid attacks which have persisted since. Allergy antigen therapy was of no avail. In February, 1933 a roentgenogram again showed soft infiltrations in both upper lobes with two cavities in the right upper lobe. In March, 1933 right artificial pneumothorax was instituted. Following this she developed atelectasis of the right lower lobe. Later she developed fluid in her right pleural space. On January 25, 1934 vaginal hysterectomy was done for persistent metrorrhagia. By June, 1934 her asthmatoid attacks were so severe that she was sent to the desert. On December 11, 1935 right oleothorax was instituted because her space was being lost.

On January 23, 1937 she was readmitted to Olive View Sanatorium with a temperature of 102°F. A roentgenogram showed far advanced pulmonary tuberculosis, fibrotic type. The right lung field was opaque. The left lung was clear except for a few discrete nodules. The oil was withdrawn and replaced with air. The right lung field cleared and no cavity was visible. She had developed an empyema on the right side, and August 24, 1937 thoracoplasty was advised for this.

On September 3, 1937 she had a routine preoperative bronchoscopic examination. There was marked stenosis of almost the entire trachea with irregularly contracted bands of fibrous tissue. About half way down the trachea an 8 mm. bronchoscope would not pass. A 5 mm. bronchoscope was substituted. The carina was obliterated. The right main bronchus was reduced to a mere slit. The left main bronchus was markedly stenosed at its orifice. There was no ulceration. She was markedly dyspnoeic for three days after bronchoscopy. The thoracic surgeons decided against thoracoplasty.

She was discharged from Olive View Sanatorium in January, 1938 entirely ambulant. Her sputum has been negative on guinea-pig inoculation since August, 1933. Her empyema fluid is negative for tubercle bacilli and pyogenic microörganisms. She is very comfortable except when aspirations are too infrequent. While she is still a pulmonary cripple because of her empyema and narrowed tracheal lumen, her tuberculous tracheobronchitis has apparently been entirely healed for five years.

F. K.: No. 9323, a large Japanese single female student aged 23, was admitted to Olive View Sanatorium on January 27, 1937, from the Los Angeles County General Hospital where she had been a patient since October 8, 1936. Her exposure was to her mother who had died from pulmonary tuberculosis in 1934. She had always been in good health until she developed a cough in July, 1936. In August, 1936, she had a negative chest examination. On September 17, 1936, because of undue fatigue and slight fever, she was again examined at the University of California Hospital in San Francisco where a chest roentgenogram was taken. Mantoux was two-plus. Her sputum was positive for tubercle bacilli. While at the Los Angeles County General Hospital she had her first bronchoscopic examination which showed an ulcerative tuberculous tracheobronchitis limited to the right upper lobe bronchus.

On admission to Olive View Sanatorium, physical findings were essentially negative and she had no complaints except a productive cough. A roentgenogram showed complete atelectasis of the right upper lobe and slight bronchial thickening of the right middle lobe bronchus, but otherwise was negative. She raised three ounces of tenacious sputum daily, containing 150,000 tubercle bacilli. Her vital capacity was 80 per cent (2,600 cc.). Her sedimentation time was 32 minutes. She had an ulcerative tuberculous laryngitis.

She was first bronchoscoped at Olive View Sanatorium April 21, 1937. There were submucosal nodules throughout the trachea. The lower two and one-half inches of the trachea on the right were ulcerated with heavy, moist, red granulations extending down and encircling the right main bronchus,

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obliterating the carina on the right. The right upper lobe bronchial orifice was completely destroyed. The left bronchial tree was normal.

The first part of August, 1937 she developed dyspnoea. On August 19, 1937 she was bronchoscoped again. The granulations and ulcerations had entirely disappeared, being replaced by smooth fibrous tissue. The right main bronchus was stenosed to 4 mm. diameter, and the carina was obliterated. Dyspnoea persisted. On December 8, 1937 she was again bronchoscoped. No granulations or ulceration were seen. The right main bronchus, now stenosed to 2 mm. diameter, was dilated with a no. 16 French bougie. Her dyspnoea was relieved.

Her sputum now is negative on culture and guinea-pig inoculation, she is free from dyspnoea, and her larynx has returned to normal.

In this patient tuberculosis was apparently limited to the tracheobronchial tree. Her tuberculous tracheobronchitis is apparently healed, without cauterization. We were fortunate in being able to observe this lesion bronchoscopically throughout almost its entire course.

S. Z.: No. 8965, a married Mexican male, aged 27, who had been a wool and skin dealer for seven years, was admitted to Olive View Sanatorium July 27, 1936. His onset was in 1930 with cervical adenitis, colds and pleurisy. He continued to work until 1936, when he was admitted to the Los Angeles County General Hospital, where left artificial pneumothorax was established. On admission to Olive View Sanatorium he was afebrile, raising from nothing to three ounces of sputum daily, which was positive for tubercle bacilli. His sedimentation time was 60 minutes and vital capacity 35 per cent (1,600 cc.). Roentgenological study diagnosed far advanced pulmonary tuberculosis, type undetermined, with left pneumothorax. There was a small cavity in the first interspace. The right lung was clear. In July, 1937 he developed tuberculous laryngitis. In November, 1937 bronchoscopy was requested because of persistently positive sputum with cavity no longer visible.

The first bronchoscopy was performed November 10, 1937. The trachea showed submucosal nodules throughout. The lower two and one-half inches on the left were ulcerated with thick papillomatous granulation tissue extending into its lumen. The left main bronchus was so filled with these same granulations that its lumen was about 1 mm. in diameter. The carina was obliterated by these heavy granulations. The right bronchial tree was normal. All of this ulcerated mass was cauterized with thirty per cent silver nitrate.

Four weeks later, December 8, 1937, he was bronchoscoped again. At this time the granulations were over the same area but were now very fine, dotting a smooth surface. They were again cauterized. On January 27, 1938 and May 18, 1938 he was bronchoscoped again and no granulations

were present. The lower end of the trachea was stenosed to about two-thirds normal diameter, and formed a more or less straight tube with the right main bronchus. There was no carina. The left main bronchus was about 1 mm. in diameter and contained no granulations. His sputum on October 18, 1937 contained two-thirds of a million tubercle bacilli daily, but has been negative on culture and guinea-pig inoculation since November, 1937. Roentgenogram shows no cavity. He continues to take left pneumothorax refills. His larynx has returned to normal.

The next three case reports were selected to show that tuberculous tracheobronchitis does not necessarily contraindicate major thoracic surgery.

J. G.: No. 7616, a single white female stenographer, aged 24, was first admitted to Olive View Sanatorium July 11, 1934. Her onset was insidious one year before, and exposure to tuberculosis was unknown. On admission she was running a septic temperature up to 101°F. She was raising one ounce of sputum daily which was positive for tubercle bacilli. Her sedimentation time was twelve minutes, and her vital capacity was 1,500 cc. Roentgenographic diagnosis was far advanced pulmonary tuberculosis, exudative type. There were two large cavities in the left upper lobe, the largest five and one-half by twelve centimetres in diameter. The remainder of the left lung was filled with soft, coarse infiltration. There was some soft infiltration in the right upper lobe.

On September 25, 1934 her left phrenic nerve was crushed. On March 20, 1935 her left phrenic nerve was extirpated, and she had a left scaleniotomy. From September 10, 1935 to January 14, 1936 she had a four-stage left thoracoplasty.

On July 14, 1936 she was first bronchoscoped because of persistently positive sputum in spite of no visible cavities by roentgenogram. There was an ulcerative tuberculous tracheobronchitis involving the lower end of the trachea on the left and the left main bronchus. In September, 1936 she left the Sanatorium.

On June 7, 1937 she was readmitted to Olive View Sanatorium because her sputum was still positive for tubercle bacilli. Roentgenographic study showed her left lung well collapsed by thoracoplasty. The left lung field was opaque. There was no cavity shown by a Bucky film. On June 23, 1937 she was bronchoscoped. The lower three centimetres of the trachea on the left were ulcerated, with heavy granulations. The left main bronchus was completely occluded and the carina obliterated by these granulations. All of the ulcerated area was cauterized. Since that date she has had bronchoscopic cauterization six times. On March 9, 1938 there was only a small bleb of granulation tissue at the site of the left main bronchus. On June 9, 1938

it was questionable that any active lesion remained. There is a slight stenosis of the lower end of her trachea. Her sputum has been negative on culture and guinea-pig inoculation since August, 1937.

K. W.: No. 9052, a white married male bank teller, aged 32, was admitted to Olive View Sanatorium September 8, 1936. His exposure to tuberculosis is unknown. His onset was haemoptoic in October, 1927, at which time he had sanatorium care for nine months. He then worked until January, 1936 when he again entered a sanatorium because of cough and loss of weight. On admission to Olive View Sanatorium he was running a septic type temperature. He raised five ounces of sputum daily which was positive for tubercle bacilli. His sedimentation time was 20 minutes, and his vital capacity was 28 per cent (1,200 cc.). Roentgenological study diagnosed far advanced pulmonary tuberculosis, with stenosis of the left main bronchus and bronchiectasis of the left lung. There was atelectasis of the left lung, with cavitation in the left upper lobe. There was fibrotic infiltration of the right upper lobe. Left thoracoplasty was advised.

On October 14, 1936 bronchoscopy showed a normal trachea, carina and right bronchial tree. The left main bronchus was stenosed. About one and one-half inches below the carina its lumen narrowed to 2 mm. This was dilated with a no. 16 French bougie. There were no ulcerations or granulations.

From December 29, 1936 to March 3, 1937 he had a three-stage thoracoplasty. On April 8, 1937 he suddenly developed a septic type temperature to 102°F., with polymorphonuclear leucocytosis, and marked dyspnoea. Symptoms and findings persisted until he was bronchoscoped April 14, 1937. A large amount of pus was aspirated from below his stenosed left main bronchus. His white blood count and temperature then returned to normal.

On February 16, 1938 he was again bronchoscoped. Bronchoscopic findings were similar to his first examination sixteen months before. Lipiodol was injected below his stenosed left main bronchus, and a bronchogram taken which showed cylindrical and saccular dilatation of the bronchi of both the upper and lower lobe bronchi. At present he feels well and has been discharged to his home. He raises two ounces of sputum daily which has been negative for tubercle bacilli since March 1, 1937.

A. P.: No. 8862, a white female, separated, waitress and taxi dancer, was admitted to Olive View Sanatorium June 4, 1936. Her exposure to tuberculosis was for one year to her husband. The onset was insidious in 1934, with cough, expectoration and haemoptysis. She was admitted to the Los Angeles County General Hospital in March, 1936, where left artificial pneumothorax was established. On admission to Olive View she was running a septic type temperature up to 102°F., had four ounces of sputum daily which was positive

for tubercle bacilli and was occasionally blood-streaked. Her sedimentation time was 7 minutes. Her vital capacity was 32 per cent (1,000 cc.).

Roentgenographic study diagnosed far advanced pulmonary tuberculosis, exudative type. There was a large left basal pneumothorax pocket. The left apex was adherent and contained two cavities measuring about 2.5 cm. each. The right upper lobe had a moderate amount of soft infiltration, but no cavitation. Pneumothorax refills were continued every two weeks and her left phrenic nerve was crushed August 11, 1936. In March, 1937 left thoracoplasty was advised but, because a Bucky film showed a narrowed left main bronchus, the chest surgeon requested first to have her bronchoscoped to see how much stenosis there was, and its location.

She was bronchoscoped May 26, 1937. Bronchoscopy showed the trachea, carina and right bronchial tree normal. The left main bronchus showed a gradual narrowing by contracted bands of fibrous tissue, reaching an apex about 1.5 cm. below the left upper lobe bronchial orifice where the stenosis would barely admit a no. 12 French bougie. There was no ulceration and no granulation tissue.

She had a left thoracoplasty in three stages from July, 1937 to September, 1937 with successful recovery. At present her sputum is negative. The infiltration in the right upper lobe is fibrotic. The left lung is opaque, and no cavity can be seen by Bucky film.

Our experience has been that the majority of tuberculous mucosa ulcers in the tracheobronchial tree heal much more rapidly and with less stenosis with cauterization than when left untreated. Many of these ulcerations remain active for months or years, gradually producing more stenosis and excreting tubercle bacilli into the sputum, if left untreated. We have used with satisfactory results both thirty per cent silver nitrate as used by Tuttle (3), and the Samson bronchoscopic high frequency cautery. There are a few ulcers which are too acute and rapidly spreading for cauterization. Ulcers located in smaller bronchi sometimes cannot be successfully cauterized.

When stenoses prevent adequate drainage of secretions or cause dyspnoea, symptoms are almost always relieved for weeks or indefinitely by aspirating the blocked secretions and dilating the stenosis with a flexible bougie. Localized areas of stenoses are more easily dilated than a stenosis of an entire bronchus. To cut a thin-walled stenotic ring we have used the Samson high frequency cautery as advised by Jones (13).

We have used no local therapy for submucosal tuberculous tracheobronchitis. At present direct ultraviolet irradiation, as admitted by Kernan (14), is impractical. We had one patient in which deep roent-

genotherapy gave excellent results. Submucosal nodules were quickly destroyed with no resulting stenosis, and the patient was markedly relieved symptomatically. In a series of cases of all types of tuberculous tracheobronchitis, given high vitamin C intake for one year, at Olive View Sanatorium there was a higher percentage of improvement than in the control group who were on a low vitamin C diet.

We have found complications of bronchoscopy in tuberculous patients to be rare. In our series to date, three patients died within three weeks following bronchoscopy, and one patient developed a spread of infiltration following bronchoscopy. We know now that these patients were too sick for bronchoscopy. Two patients developed cardiac depression during bronchoscopy, but recovered immediately. They were both chronic asthmatics. One patient dislocated his mandible, a frequent occurrence with him. One patient received a broken denture.

SUMMARY AND CONCLUSIONS

Tuberculous tracheobronchitis, while recognized many years ago, has not received adequate study until recently. Types of lesions, prognosis and the value of local treatment are now the subject of much discussion, and in time we will have a common understanding. Realization that bronchoscopy is not detrimental to patients with tuberculosis was the first step in this progress.

From our study of 516 patients bronchoscoped, we found 132 patients with tuberculous tracheobronchitis. We have found that a high percentage of these patients with tuberculous tracheobronchitis have roentgenological evidence or symptoms which lead us to suspect tuberculous tracheobronchitis before bronchoscopy. The number of patients bronchoscoped at Olive View Sanatorium has increased rapidly in the past two and one-half years.

Many patients with tuberculous tracheobronchitis make good recovery. We have seen 17 patients with apparently healed tuberculous tracheobronchitis. (Three case reports.)

Tuberculous tracheobronchitis does not necessarily contraindicate major thoracic surgery or other collapse therapy, though patients scheduled for major thoracic surgery should first have the benefit of a bronchoscopic examination. (Three case reports.)

Most patients with tuberculous tracheobronchitis make better progress with local treatment than without.

Complications of bronchoscopy in the tuberculous are rare.

REFERENCES

(1) ELOESSER, L.: Bronchial stenosis in pulmonary tuberculosis, Amer. Rev. Tuberc., 1934, *30*, 123; Jour. Thoracic Surg., 1931, *1*, 194, and 1932, *1*, 270, 373, 485.

(2) SAMSON, P. C.: Tuberculous tracheobronchitis, Amer. Rev. Tuberc., 1936, *34*, 671. Diagnosis, treatment and prognosis in tuberculous tracheobronchitis, Jour. Thoracic Surg., 1937, *6*, 561.

SAMSON, P. C., BARNWELL, J., LITTIG, J., AND BUGHER, J. C.: Tuberculous tracheobronchitis, Jour. Amer. Med. Assn., 1937, *108*, 1850.

(3) WARREN, W., HAMMOND, A. E., AND TUTTLE, W. M.: The diagnosis and treatment of tuberculous tracheobronchitis, Amer. Rev. Tuberc., 1938, *37*, 315.

(4) MYERSON, M. C.: The limitations of bronchoscopy in the treatment of tuberculous tracheobronchitis, Quart. Bull. Sea View Hosp., 1938, *3*, 227.

(5) JACKSON, C. V., AND JACKSON, C. L.: Bronchoscopy, esophagoscopy and gastroscopy, ed. 3, Philadelphia, Saunders, 1934.

(6) CLERF, L. H., AND PUTNEY, F. J.: Peroral endoscopy, Arch. Otolaryng., 1938, *27*, 347.

(7) LOUIS, P. C. A.: Researches on phthisis, ed. 1, Paris, France, 1825; ed. 1, translated by CHAS. COWAN, Edinburgh, 1836; ed. 2, translated by W. H. WALCHE, London, Sydenham Society, 1844.

(8) POWELL, R. D.: Diseases of the lungs, Philadelphia, Blakeston, 1893.

(9) CORNET, G.: Tuberculosis, Philadelphia, Saunders, 1904.

(10) Descriptive Catalogue of the Museum of the British Congress on Tuberculosis, held in London, July 22 to July 26, 1901, compiled and edited by W. JOBSON HORNE, M. D., Honorary Secretary to the museum committee, printed by Aldard and Son, London and Darking, 1901, (Specimen 137–145).

(11) REICHLE, H. S., AND FROST, T. T.: Tuberculosis of the major bronchi, Amer. Jour. Path., 1934, *10*, 651.

(12) BURGHER, J. C., LITTIG, J., AND CULP, J.: Tuberculous tracheobronchitis, Its pathogenesis, Amer. Jour. Med. Sc., 1937, *193*, 515.

(13) JONES, J. C.: Personal communication.

(14) KERNAN, J. D.: Tuberculosis of the trachea and main bronchi, Ann. Otol., Rhin. & Laryng., 1937, *46*, 763; Laryngoscope, 1937, *47*, 777.

PLEURAL EFFUSION[1]

Its Prognosis in Patients Showing Little or No Parenchymal Involvement

FRANCIS B. TRUDEAU[2]

For many years it has been noted that the pulmonary tuberculosis in which pleurisy with effusion was an early recognized feature has a relatively benign course. This beneficial result is undoubtedly due, at least in part, to the added rest given the lung by the compression brought about by the presence of the fluid. Some years ago in going over 500 consecutive admissions to the Trudeau Sanatorium we found that, of 73 patients who had had wet pleurisy, 67 per cent were well and working, and 14 per cent had died over a period of five years, as compared with 59 per cent who were well and 17 per cent dead among those in whom this symptom had not occurred.

This is not the type of case, however, to be discussed in this paper, for, in the above 500 cases, definite pulmonary tuberculosis, for which they were under treatment, could be demonstrated in the vast majority of the patients. I wish here, however, to discuss the usual type of wet pleurisy which comes on, as it were, "out of the blue," with no premonitory symptoms, in an apparently healthy individual and then, after the absorption or removal of the fluid, the X-ray examination fails to reveal sufficient evidence to warrant a definite diagnosis of pulmonary tuberculosis. In this type of case are we actually dealing with pulmonary tuberculosis, and what may be the future outlook of such a patient?

No doubt most of us agree with Fenton (1), who states, "Whether dry or with effusion, pleurisy is to be regarded as the manifestation of the activity of the tubercle bacillus. Whether this is always so or not it is, from the point of view of the patient, the only safe view." This author states that in about 60 per cent of patients with wet pleurisy, regardless of X-ray findings, the causative factor of the infection is not demonstrated and the patients do not develop tuberculosis.

[1] Read before the American Clinical and Climatological Association in Atlantic City, May 2, 1938.

[2] Saranac Lake, New York.

Gaardi (2) finds that tuberculosis was the cause of death in 29 out of 35 fatalities in his group of 126 patients who had pleurisy with effusion and in whom all definitely active or advanced pulmonary tuberculosis had been excluded.

Burrell (3) states, "Tuberculous effusion must be taken as evidence of disease in the lung and in some 40 per cent of the cases active pulmonary tuberculosis develops."

Heise and Brown (4) in studying 121 cases of wet pleurisy found that "three per cent occurred in nontuberculous, 21 per cent in 'suspects,' 10 per cent in minimals, 58 per cent in moderately advanced and 8 per cent in far advanced cases. . . . About three-fourths of the pleurisy with effusion occurred when definite pulmonary tuberculosis was present." It is the future behavior of the remaining 25 per cent, or the cases in which no definite pulmonary tuberculosis was demonstrable by X-ray, that we wish to bring to your attention. Certainly we will all agree that the immediate treatment of these cases after the development of the effusion has much to do with their prognosis, and it must be remembered that the series of patients that we are here reporting have all received sanatorium treatment, rather than being allowed to return directly to work following the cessation of their symptoms.

I wonder if Anderson (5) gives us the point of view of most of the various life insurance companies in this country when he concludes his excellent article by saying that although he feels that ordinary pleurisy with effusion is practically always tuberculous, it represents a relatively light and curable phase of disease. He believes that all recovered cases over thirty years of age, who have regained their normal weight, in whom there is no family history of tuberculosis, after five years may be accepted at standard rates.

Dublin and Marks (6) of the Metropolitan Life Insurance Company do not go quite as far as this when they state, "At ages over 35, a few cases may be granted standard insurance after five years have elapsed."

In trying to shed a little more light on this debated subject, we have reviewed and traced all those patients who had been sent to Trudeau Sanatorium because of wet pleurisy in whom the X-ray film, after the removal or absorption of the fluid, was read as negative, doubtful, or questionable as far as parenchymal involvement was concerned. Fifty-four patients came within this group; but, in going over the records, 29 others were found in whom slight parenchymal involvement, not extending below the second rib, was demonstrated by X-ray. Rather

than discard these latter 29 cases, we decided to study them separately, thus giving us a total of 83 cases on which to report.

The patients with negative or questionable X-ray findings have been designated as group I, while group II consists of the 29 patients in whom the slight X-ray findings referred to were present.

The average age of these patients was practically identical with the age of the average patient admitted to the Sanatorium with the exception that fewer of them fell into the older group. In group I there were 12 patients under twenty-four, 41 patients between twenty-four and forty, and only one over forty. Group II contained 8 under twenty-four, 18 between twenty-four and forty and 3 over forty; thus giving us a total of 20, 59 and 4 cases respectively in the age groups just mentioned. In this series we find women much more frequently affected than men, as group I consists of 20 men and 34 women, while in group II these figures are 9 and 20, respectively, or a combined total of 29 men and 54 women.

Our study shows that there seems to be little predilection as to the side affected. In group I the pleurisy occurred on the right side in 20 and on the left in 33 cases, while in group II 4 more appeared on the right than on the left, the figures being 16 and 12 respectively. Each group included one bilateral case. The totals of the two groups were, therefore, right 36 cases, left 45 cases, both sides 2 cases.

Many of the patients had had a thoracocentesis before coming to us and we found that 37 cases in group I and 20 cases in group II, or a total of 57 patients (69 per cent), had received this form of treatment. An analysis of the fluid in these 57 cases in which it was withdrawn might prove of value from a prognostic standpoint, as Gaardi (2) reports that, out of 79 cases in which pleural effusions were inoculated into guinea pigs, 56.1 per cent recovered whose fluid was negative to this test, whereas this was true of only 36.3 per cent of his series in which the guinea pigs developed tuberculosis.

On the other hand, Pinner and Moerke (7) conclude that neither chemical nor cytological nor serological data afford *per se* dependable diagnostic or prognostic criteria.

Unfortunately in our series no report was to be found of the examination of the fluid in 38 of the total of 57 previous tappings; 27 of these "no report" cases being in group I and 11 in group II. In the remaining cases in whom some report was recorded, we find the following: guinea pig positive in only one case, while negative results were reported in 11

cases; 6 in group I and 5 in group II. In 3 cases the results were questioned and in 2 cases in each group the fluid was reported simply as "negative." I regret that the bacteriological study in this report is of so little value.

In accordance with the statistical studies of Brown and Heise (8), for many years we have taught in our postgraduate school that a negative diagnosis of pulmonary tuberculosis could be based on the absence of all of the following points:

1: History of haemoptysis of a dram or more of blood
2: History of simple wet pleurisy
3: Persistent, moderately coarse râles in the upper third of the chest
4: Parenchymal changes shown in the X-ray films
5: Tubercle bacilli in the sputum

As all cases here being reported have had wet pleurisy, and the X-ray findings have been described, let us make an analysis of the remaining three of the five cardinal points just mentioned.

We find that 3 cases, all in group I, gave a history of haemoptysis. Four patients in our first group and 6 in our second had persistent râles in the upper third of their chests. In 7 cases tubercle bacilli were found in the sputum; 4 of these cases occurring in group I and 3 in group II. Of these 7 cases, the sputum was found to be positive in 3 only before coming to us, while in 3 patients tubercle bacilli were found during their Sanatorium stay. In one case tubercle bacilli were found prior to coming to us and also while the patient was in the Sanatorium.

It has been previously brought out that the duration of the treatment immediately following simple effusion had much to do with the prognosis of the case. The shortest length of time that any of these patients here reported remained in the Sanatorium was 37 days, while the longest that any of them continued treatment was 407 days; the average duration for all patients in both groups was a few days over four months.

Their follow-up record extended over a period of from three to twenty-five years divided as follows:

7 patients, 5 in group I and 2 in group II, were followed from three to six years
40 patients, 20 in each group, from six to ten years
27 patients, 20 in group I and 7 in group II, from ten to twenty years
9 patients, all in group I, from twenty to twenty-five years

RESULTS

Before we consider the late results of these cases let us take up the record of relapses. The difficult part of this is to define what we mean by relapse. In our yearly questionnaire which we send to all expatients is the question, "Have you relapsed within the past year?" Often this is simply answered by "Yes" or "No" but frequently certain symptoms, laboratory or X-ray findings are described and we are left to draw our own conclusions.

In group I, 4 relapses are recorded, one of these being questioned as it occurred fifteen years after discharge and the patient has been well for the past six years. Of the remaining 3, we find that one occurred two years after discharge but since has reported "well" for eighteen consecutive years; another broke down five years after discharge but has been well for the past three years; while the remaining patient was quite remarkable in that she remained "well" for seven years after discharge, then developed active disease with a positive sputum. A thoracoplasty was done, which was so successful that she has since had a baby and her reports are now again coming in marked "well," thirteen years after her discharge.

In group II the frequency of reported relapses is four times that of group I. There were 8 such cases and the certainty of the relapse was much more definite, as in 4 patients a positive sputum was recorded. Two patients reported increased X-ray shadows. One had a return of her effusion and in the remaining case the symptoms seemed to indicate a return of the disease. Both groups therefore showed a total of 12 cases, or 14 per cent, which were recorded as having relapsed, although certainly several of these seem rather doubtful.

Our late results seem too optimistic to be true, for, of the 54 patients in whom the X-ray films were either negative or doubtful, 40, or 91 per cent, were well and working or able to work. One was reported simply "living" with only 4 (7 per cent) reported as dead. Among our 29 cases in group II, with definite though slight parenchymal involvement of the apex but not extending below the second rib, 25 (86.2 per cent) were well, 3 (10.3 per cent) were living while only one (3.4 per cent) had died. Combining these groups for our entire series of 83 cases, 74 (89 per cent) were reported well, 4 (5 per cent) living and 5 (6 per cent) dead after an interval of from three to twenty-five years. In a personal communication (9) Louis I. Dublin points out that this group is a very small one and the probable error in the result is quite

large. However, he made a rough estimate of the number of deaths which would be expected to occur in the group on the basis of recent population mortalities. This estimate shows that the mortality in the group was about normal.

In closing, the analysis of the causes of death might be instructive. In the one death in group II, tuberculous meningitis, occurring three months after discharge, was given as the cause. The four deaths occurring in our first group were reported as follows:

1: Pulmonary tuberculosis (?) ten years after discharge. The patient had remained well for nine years after leaving the Sanatorium, and had stated that an X-ray film taken one year previous to death showed nothing new. I doubt if pulmonary tuberculosis was the cause of death in this case.
2: Tuberculosis of the kidney, fourteen years after discharge
3: Acute intestinal obstruction, three years after discharge
4: Cause unknown

In none of the five deaths occurring in this series was pulmonary tuberculosis given definitely as the cause.

CONCLUSIONS

1. A total of 83 cases of simple pleurisy with effusion have been analyzed. In 54 of these cases (group I) the X-ray evidence was not sufficient to warrant a diagnosis of pulmonary tuberculosis. In the remaining 29 cases (group II) slight parenchymal involvement, never extending below the second rib, was noted.

2. After following these cases from three to twenty-five years subsequent to discharge, we find that in group I there have been only four reported "relapses" with at least one of these very doubtful, while in group II, eight relapses occurred.

3. A total of 74 (89 per cent) of our 83 cases were reported "well and working;" 4 (5 per cent) as "living," while only 5 (6 per cent) had died.

4. In none of the five deaths was pulmonary tuberculosis definitely given as the cause, although tuberculosis of other organs was reported to have caused the death of two of these patients.

5. The prognosis of pleurisy with effusion with either negative, doubtful or extremely slight apical pulmonary findings by X-ray is excellent in patients receiving at least four months of sanatorium care; in fact, it is practically as good as the normal adult population in the same age group.

The author is indebted to Miss Joan Brown, Flushing, New York, for valuable assistance in reviewing records.

REFERENCES

(1) FENTON, W. J.: Simple pleurisy with effusion, Tubercle, 1937, *18*, 337.
(2) GAARDI, F. W.: Prognosis of pleurisy with effusion, Jour. Amer. Med. Assn., 1930, *95*, 249.
(3) BURRELL, L. L. T.: Causes and results of pleural effusion and empyema, Brit. Jour. Tuberc., 1933, *27*, 122.
(4) HEISE, F. H., AND BROWN, L.: Diagnostic and prognostic significance of pleurisy in pulmonary tuberculosis, Amer. Rev. Tuberc., 1928, *17*, 500.
(5) ANDERSON, H. B.: Concerning the tuberculous nature of pleurisy from the life-insurance standpoint, Ibid., 1928, *17*, 147.
(6) DUBLIN, L. I., AND MARKS, H. H.: Medical selection of cases with a history of pleurisy, Read at the forty-third annual meeting of the Association of Life Insurance Medical Directors of America, October 27–28, 1932.
(7) PINNER, M., AND MOERKE, G.: Pleural effusions. Laboratory findings and clinical correlations, Amer. Rev. Tuberc., 1930, *22*, 121.
(8) BROWN, L., AND HEISE, F. H.: The value of the Trudeau Sanatorium's five diagnostic criteria of pulmonary tuberculosis in negative diagnosis, Ibid., 1924, *9*, 398.
(9) DUBLIN, L. I.: Personal communication, April 20, 1938.

TUBERCULIN ANERGY IN CASES WITH PULMONARY CALCIFICATIONS[1]

PAUL D. CRIMM AND DARWIN M. SHORT

This study was prompted by the findings in a recent investigation (1) of the comparative efficiency of the tuberculins, in which routine roentgenograms of the chest revealed cases with obvious Ghon's tubercle without tuberculin skin sensitivity to diagnostic doses. Nelson, *et al.* (2) recently reported 16.9 per cent of 160 cases with negative tuberculin tests but positive roentgenological evidence of calcification. However, they made no mention of the probable cause or significance of this observation. This report is concerned with diagnostic doses of tuberculin and not with absolute anergy. Frequently cases anergic to diagnostic doses will react to doses of 5 or 10 mg. of tuberculin.

All cases in the present series had at some previous time acquired the primary infection of tuberculosis, as evidenced by focal areas of calcification. Other causes of shadows simulating the calcified tubercle of primary infection have been proved by Frimann-Dahl and Waaler (AMERICAN REVIEW OF TUBERCULOSIS, 1938, *37*, 117) who found calcium in nontuberculous lesions. Each case in the present series was tested with intracutaneous tuberculin in graded doses, both with OT and PPD, six to nine times during a four-year period. All tuberculin tests were negative. In the previously mentioned study (1) 1,003 cases were examined. Of this number 32.5 per cent had positive Mantoux tests. There were 153 cases of anergy (loss of allergy) to the tuberculins. Subsequent examinations make the total 1,384 cases examined by this method, with 191 cases that did not react at all to all intracutaneous diagnostic doses of tuberculin (figure 1).

Following the above findings, all roentgenograms of the anergic cases were reviewed[2] (figure 2) in order to eliminate any questionable cases of calcification. To minimize the questionable cases of calcification the

[1] From the Research Laboratories, Boehne Tuberculosis Hospital, Evansville, Indiana.

[2] Courtesy of Dr. J. W. Strayer, Medical Director and Superintendent, William Ross Sanatorium, Lafayette, Indiana.

following criteria were used: (A) Circular, homogeneous areas were not considered as being calcification, unless located in the periphery where the size precluded its being a cross section of a vessel. (B) Areas irregular in outline, multi-angular or crenated, were considered to be calcification. (C) Calcifications due to haematogenous spread are more regular and uniform, but their distribution causes no doubt as to their aetiology. (D) A greater degree of shadow hardness differentiates the calcifications from the less intense shadows of blood vessels. In this group of cases the areas of calcification were usually in series and in the main were complete complexes.

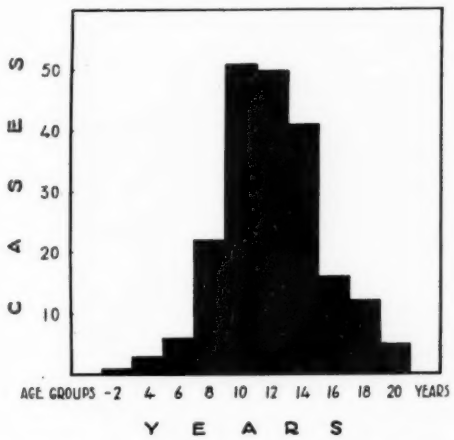

FIG. 1. Age distribution of 191 cases with pulmonary calcifications and anergy to tuberculin.

Two and/or three years following the first examination the same anergic group was retested with the second strength of PPD (0.005 mg.) and an intermediary strength of PPD (0.001 mg.). In each case in this series the final simultaneous doses of the two tuberculins were equivalent to 2 mg. of OT. In the reëxamination, four cases clearly demonstrated either the return of allergy to tuberculin or a reinfection. These cases were all living in households harboring tuberculosis, but no active disease was noted.

In reëxamining 75 cases of low grade (one-plus and two-plus) reactors of the same series and age range, 18.0 per cent demonstrated the complete "loss of allergy" upon examination two to three years later. His-

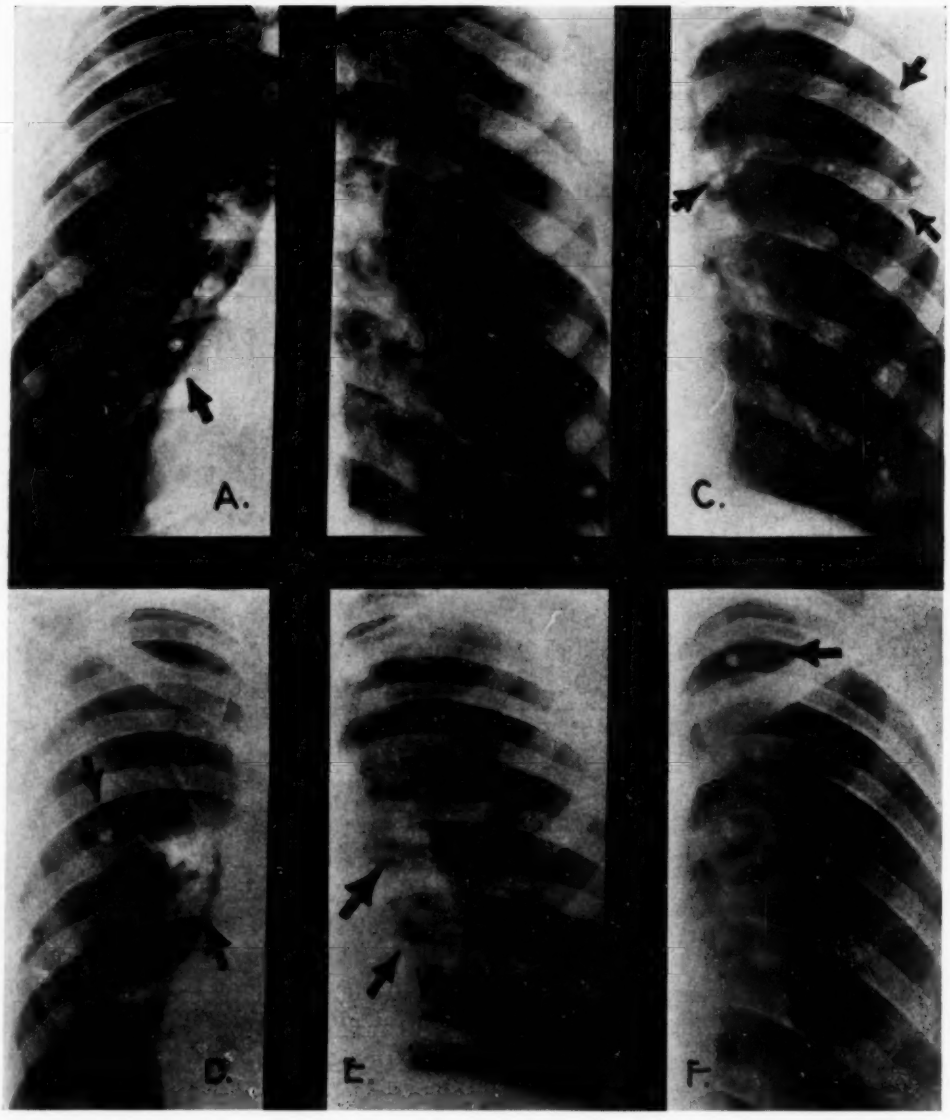

FIG. 2. Representative roentgenograms of tuberculin anergic cases showing type, distribution and character of calcifications.

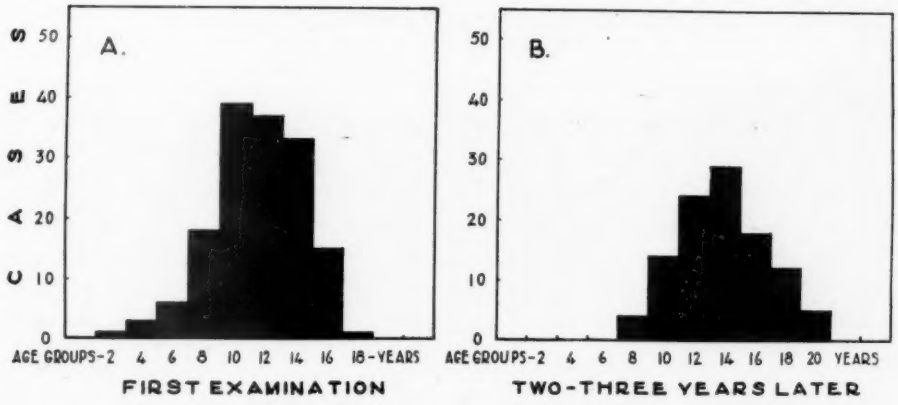

FIG. 3. A: Age distribution of 153 tuberculin anergic cases at first examination. B: The same anergic cases reëxamined two and three years later, showing age distribution, loss of cases and the progression of peak distribution to the next age group.

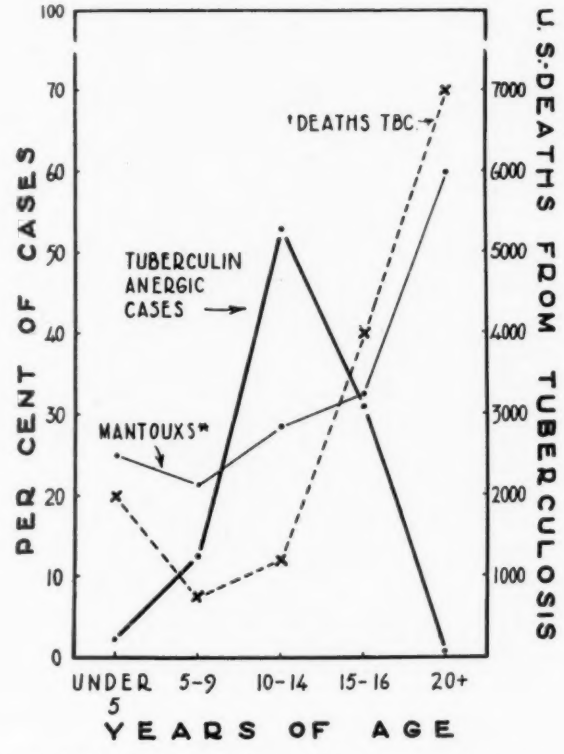

FIG. 4. Diagram showing age distribution of tuberculin anergic cases.
† U. S. deaths from tuberculosis (N. T. A. B-234, 1937).
* Mantoux-positive cases (Whitney and McCaffrey, 1937).

tograms (according to age distribution) of the first and subsequent examinations of the anergic cases show a progression of the peak according to the interval between the examinations (figures 3A and B). These findings present the question of the possibility of the anergic state being a part of the evolution of the primary tuberculosis complex. This accounts for the low incidence of Mantoux reactors and the low death rate in this age range. Another possibility, suggested by the frequency of anergy in contact cases, is that of desensitization by frequent subreactionary doses of tubercle bacilli.

The anergic cases are of interest when examined according to the age distribution and compared with results of the recent national final report on PPD by Whitney and McCaffrey (3) and the current death rate (4) for the same age groups. The peak of the anergic cases coincides with the trough of the Mantoux-positive reactors and national death rate curves (figure 4). The relationship of the data represented by these curves presents a phase of the tuberculosis problem which may be reciprocal. This reciprocal relationship is only suggested and by no means conclusive, owing to the limited number of cases which are compared with other larger groups.

In the present series, 13.8 per cent of all cases examined were anergic to the doses of tuberculins used. In this locality the ratio of anergic cases to Mantoux-positive cases is about 1:2.2 for this age range. The incidence of tuberculin-anergic cases will probably vary according to locality, as will the ratio of anergic cases to Mantoux-positive cases. These preliminary results are presented in the hope of provoking similar studies in other localities.

SUMMARY

1. Of 1,384 cases tested with OT and PPD, 191 cases showing roentgenological evidence of pulmonary calcification were anergic to diagnostic doses of tuberculin.

2. Over a four-year period 4 cases manifested either a return of allergy or reinfection as indicated by the tuberculin tests. Fourteen cases were observed to develop a loss of allergy.

3. The possibility of a reciprocal relationship is suggested between the curve of tuberculin reactors and the death rate, as compared with the curve of the anergic cases.

4. Thirteen and eight-tenths per cent of the cases examined were anergic, with a 1:2.2 ratio for anergic cases to Mantoux reactors.

REFERENCES

(1) Crimm, P. D., Short, D. M., and Wood, H. E.: Qualitative and quantitative evaluation of Old Tuberculin and Purified Protein Derivative (P.P.D) with X-ray correlation on 1,003 children, Tr. Natl. Tuberc. Assoc., 1937.

(2) Nelson, W. E., Mitchell, A. G., and Brown, E. W.: The intracutaneous tuberculin reaction associated with calcified intrathoracic lesions, Amer. Rev. Tuberc., 1938, *37*, 311.

(3) Whitney, J. S., and McCaffrey, I.: A summary of the results of group tuberculin-testing with P.P.D. (Purified Protein Derivative) in the United States, Final report of the National Tuberculosis Association, Amer. Rev. Tuberc., 1937, *35*, 597.

(4) National Tuberculosis Association, Deaths from tuberculosis and other leading causes, United States, 1937, B-234, November 6, 1937.

VARIATIONS IN LEUCOCYTES[1]

Studies on Tuberculous Patients under Basal and Active Conditions

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Numerous investigators have stressed the correlation between the leucocytic blood picture and the evolution of the pathological lesions in tuberculosis. Webb and coworkers (1) observed the relationship between lymphocytosis and increased resistance in tuberculosis; Murphy and associates (2) later confirmed this work.

It remained for Sabin, *et al.* (3) to elucidate the rôle of the monocyte in tuberculosis and to demonstrate that progression of the disease was associated with an increase in the number of monocytes in the peripheral blood. In addition, they established the monocyte-lymphocyte ratio as a convenient mathematical expression to describe the immediate pathological status of the tuberculous lesion. Their work has been repeatedly confirmed by other investigators (4 to 7).

Medlar (8) in an excellent series of papers emphasized the relation of the neutrophile to caseation and evaluated the leucocytic blood picture in tuberculosis. This evaluation may be stated, in brief, as follows: the lymphocyte is the predominating cell in healing, the neutrophile in caseation and abscess formation and the monocyte in new tubercle formation, while the total leucocyte count roughly reflects "the volume of deranged tissue with which the leucocytes have to cope" (9).

The work thus briefly summarized constitutes a distinct advance in our understanding of tuberculosis and is of definite diagnostic and prognostic value in cases of known tuberculosis. This latter thought has been well stated by Griesbach (10) who said that "the serial prosecution of hemogram forms or curves, which are naturally non-specific for tuberculosis but absolutely pathognomonic, makes possible an accurate insight into the individual phases of the physical combat against infection and permits us to establish the prognosis better than any other method of investigation."

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It is needless to say that the proper application, interpretation and correlation of the leucocytic picture in tuberculosis demand accurate and repeated blood counts over a prolonged period of time. Similarly, Wiseman and Doan (11) have pointed out that "emphasis, finally, is to be placed upon repeated examinations in the same patient, with exquisite technical precision rather than a single casual observation, if full significance of any procedure is to be realized."

It is, therefore, of some importance to determine any variations in the leucocytic count due to factors unrelated to the tuberculous infection, such as food, exercise, emotional disturbances, etc., and to determine whether these variations, if any, are sufficiently significant to affect the essential interpretation of the leucocytic count in tuberculosis. Abundant work on the daily variations of the leucocytes has been done in normal individuals; for a partial review of this work the reader is referred to the excellent paper of Garry and Bryan (12). However, there have been few such studies on leucocytic variations in tuberculous patients. Whatever investigations have been done come chiefly from Kaminsky (13) and Medlar (14).

Kaminsky (13a) reported studies on 50 tuberculous patients on each of whom one "basal" and one "activity" count were performed; the term "basal" referred to that state following a one-hour rest in bed, while by "activity" was meant that state following a short walk. The technique used in the determination of the total leucocytic count was to calculate the number of cells in the four large corner squares of the counting chamber; the differential counts were derived by counting 200 cells. Kaminsky found that 38 cases showed an increase in the total count following exercise while the remaining 12 showed a decrease; prominent variations were found in the differential counts following activity, at times with increases exceeding 100 per cent in an individual cell type. Kaminsky concluded from this work that it is desirable to perform leucocyte counts in tuberculous patients under basal conditions in order to eliminate the variations observed as a result of activity. In a second paper (13b) Kaminsky reiterated the impression that leucocyte counts should be done under basal conditions.

Medlar (14) published two papers undertaking to study the extent of the variations in the leucocytes in tuberculous patients and the effect of such variations on the interpretation of the blood picture. In the first of these papers (14a) Medlar reported that in total and differential counts on 4 tuberculous patients at bed-rest taken every ten minutes

for an hour and a half, variations up to 50 per cent in the total count and 7 per cent in the differential count were observed. Medlar believed that these variations were not sufficiently significant to alter the evaluation of the leucocytic picture. In a second paper (14b) Medlar reported studies in which two "basal" and two "activity" counts were taken on 25 tuberculous individuals; he found that, while the leucocytic indices were found to be higher during activity, "the shift in the leucocytic index did not alter to an appreciable extent the pathologic interpretation of the leucocytic picture." In a study on a second group of 12 patients on whom frequent counts were taken at bed-rest and activity, similar results and conclusions were reported. The technique employed for the total white cell count was apparently the same as that used by Kaminsky, while in the differential count 400 cells were recorded.

Critical analysis of the methods used by both these workers raises considerable question as to the accuracy of the total leucocyte counts. Both Medlar and Kaminsky determined the total leucocyte count by calculating the number of cells found in the four large corner squares of the counting chember. Ponder, *et al.* (15) in a careful paper pointed out that the counting of so few cells results in a high coefficient of variation because of the irregular distribution of the cells on the counting chamber, a factor that cannot be controlled, but can be eliminated as a source of significant error if approximately 800 cells are counted. It should also be pointed out that Kaminsky performed only one "basal" and one "activity" count on a patient, so that his work is subject to high statistical error.

In view of the conflicting reports of these workers, it was deemed advisable to study this very pertinent problem. The purpose of this paper is to report the results of a study undertaken in cases of bone tuberculosis in order to determine the variations of the total and differential white cell counts taken at regular intervals during the day under basal and ordinary conditions of hospital life and to observe whether these fluctuations merit attention where the diagnostic and prognostic use of the leucocytic count in tuberculosis is attempted.

PROCEDURE

Subjects: The group of subjects used was composed of 15 patients with bone tuberculosis. Their ages ranged from 8 to 27 years; 8 of the patients were male and 7 were female. Seven had tuberculosis of the spine, 3 of the hip, 2 of the ankle, 2 of the knee and 1 of the shoulder.

Their clinical conditions presented all gradations of tuberculosis, varying from an almost completely healed lesion to an actively progressing one with abscess formation. These gradations were chosen with the purpose of obtaining a truer perspective of the leucocytic variations. These patients were afebrile for several days preceding the study and during the day of the tests.

Method: On the evening before the leucocytic study, the patient was given his usual meal and then placed in an isolated room where he remained at absolute bed-rest without food until the following noon; in this manner, basal conditions were maintained for the first half of the study. During this period of basal conditions, hourly leucocytic counts were taken from 8 a.m. to 12 noon inclusive. Immediately after the last count the patient was given his lunch, which comprised the largest meal of the day, and then returned to his ward where he was allowed to carry on the ordinary activities of hospital life, which included moving about in bed as much as was permissible, talking to wardmates, listening to the radio, drinking and, in 2 cases, walking. At hourly intervals between 1 p.m. and 5 p.m. inclusive, leucocytic counts were again taken. At 4 p.m. the subjects were given their customary meal.

Technical methods: One accurately calibrated Thoma pipette and two accurately calibrated Levy double counting chambers with Neubauer ruling were used throughout the entire study. Blood was obtained from a finger with an automatic lancet; only freely flowing blood was used.

The first two drops of blood were discarded and then thin regular smears were drawn on glass slides; these were later stained with Wright's stain. Two more drops of blood were discarded from the finger and then the blood was drawn into the pipette; the blood was diluted 20 times with 2 per cent acetic acid. The pipette was thoroughly shaken by hand for three minutes according to the method suggested by Potain (16). Immediately following this the counts were done.

One drop of the diluted blood was added to each chamber of the two haemocytometers and was allowed to settle for two minutes. The cells in the four large corner squares (each one square millimetre) of each chamber were counted; in other words, the number of cells in sixteen square millimetres was obtained and used to determine the total white count.

In determining the differential white count, 400 cells were counted; the cells were listed as neutrophiles, both segmented and unsegmented, lymphocytes, monocytes, eosinophiles and basophiles. The differential

between the monocyte and lymphocyte was followed according to the criterion used by Medlar, the monocyte being recognized by its "muddy blue cytoplasm with faint but definite granulations" (17). In all, 150 total and differential counts were done. All counts were done by the author.

Statistical studies: These were done according to the methods suggested by Davenport and Ekas (18).

RESULTS

The range of variations of the total and differential white counts and the mean leucocytic indices under basal and active conditions are represented in table 1; a statistical analysis of the results obtained in the total white cell counts is given in table 2.

It will be observed in table 2 that the average results of the total white cell counts showed a definite increase during activity as compared to the results under basal conditions; in the former, the arithmetic mean was 7,170, while in the latter the arithmetic mean was 5,764. However, it will be noticed in table 1 that the mean range of variation of the total leucocyte counts showed no significant difference between basal and active states; this point is further emphasized by the coefficients of variation which under basal and active conditions were $\pm$ 6.5 per cent and $\pm$ 8.5 per cent, respectively.

The variations observed in the total leucocyte counts under basal conditions for each individual were of such a range as to fall well within the limits of error inherent in the technique used. During activity, only one patient, case 3, presented fluctuations prominently greater than one would expect from the known inherent limits of error; this was seen in a coefficient of variation of $\pm$ 18.9 per cent.

No postprandial leucocytosis or "rhythm" of leucocytes could be detected in the results.

No striking change was observed in the average range of variation in the different types of white blood cells under the varying conditions of the study. Whatever fluctuations were found in the neutrophile count were predominantly in the form of slight increases in the percentage and absolute number of these cells during activity. This slight increase in neutrophiles was usually at the expense of the lymphocytes which, in general, decreased slightly during activity; the increase in neutrophiles was not associated with any significant alteration in the proportion of unsegmented cells. Fluctuations in the monocytes were comparatively insignificant.

TABLE 1*

Range of total and differential leucocyte counts; mean leucocytic indices

CASE	TOTAL W.B.C.	NEUTROPHILES	LYMPHOCYTES	MONOCYTES	EOSINOPHILES	BASOPHILES	MEAN LEUCOCYTIC INDEX
1	6438–7759	62–71	24–29	4.5–7	0–2	0–.5	26
	7570–8924	*71–73*	*21–24*	*4.5–7*	*0–1*	*0–.5*	*33*
2	3974–4573	40–57	33–50.5	5.5–9	0–1.25	0–1.5	7
	4274–5939	*34–51*	*43–59.5*	*5–9*	*.5–1*	*0.5–1*	*4*
3	7453–9690	58–67	19.5–34	6.5–9	3.5–6.5	1–3.5	25
	9720–13675	*60–75*	*14–25*	*6–10.5*	*1.5–2.5*	*1.5–2*	*44*
4	3829–4384	30–38	50–53	10–17	0–3	0–1	6
	4307–6193	*36–48*	*42–52*	*8–11.5*	*0–.5*	*0–.5*	*2*
5	4296–6072	54–60	31–36	6–8	.5–2.5	0–1.5	15
	4973–5860	*55–63.5*	*30–33.5*	*6–11.5*	*.5–2*	*0–.5*	*16*
6	6016–6838	70–79	17–25	4–6	0–.5	0–.5	38
	8358–8802	*69–76.5*	*16–24*	*5.5–10.5*	*0–.5*	*0–1*	*38*
7	4617–5439	39.5–47	45–52	3.5–8	1–3	0–1	3
	4806–7060	*43–51.5*	*41.5–48*	*4.5–6*	*.5–2*	*0–1*	*3*
8	4673–5861	49–59	31–42	7–8.5	0–2	0–1.5	12
	5883–7360	*49.5–60*	*32–40*	*5.5–10*	*0–3.5*	*0–1*	*10*
9	4007–4595	47–56.5	37.5–47	3–5	0–.5	.5–1	12
	5694–7470	*50.5–66*	*30–43.5*	*3–7.5*	*0–1*	*0–1.5*	*16*
10	5927–6704	41.5–51	39.5–48	5–7	1–3	0–.5	4
	7315–10656	*50–55*	*36–41*	*5–8*	*1–2.5*	*0–.5*	*8*
11	7004–9324	57.5–62	34–38.5	3–4	0–1	0–.5	13
	9756–11211	*52–65.5*	*29.5–42*	*4.5–7*	*0–1*	*0–.5*	*18*
12	4895–5610	44.5–51	42–50	4–6.5	0–.5	0	2
	5639–6560	*45–52*	*43–47*	*3–8*	*0–1*	*0–1.5*	*2*
13	7227–8103	67.5–77	12–26.5	3.5–6	0	0–.5	46
	7015–7947	*67.5–74*	*20–27*	*6–8*	*0*	*0*	*43*
14	4029–4629	44–49.5	40–48.5	4.5–8	1.5–3	0	6
	4673–6038	*51–55.5*	*37.5–40*	*3–5.5*	*2–3.5*	*0*	*9*
15	4273–4728	37–38.5	52–55.5	4–6	1.5–4	.5–1	2
	4207–5217	*34–40.5*	*49–57*	*4–6*	*1–2.5*	*0–1*	*2*
Mean	5244–6287	49.4–58	34–42	5–8	.6–2.2	.1–1	14.7
	6275–7972	*51–61*	*32–41*	*5–8*	*.5–1.6*	*.1–.8*	*16.7*

* The plain type numbers are the results of counts taken under basal conditions, while the italic numbers are the results taken during activity.

TABLE 2*

Statistical analysis of results of total leucocyte counts

CASE	NUMBER OF COUNTS	ARITHMETIC MEAN	AVERAGE DEVIATION	STANDARD DEVIATION	PROBABLE ERROR OF MEAN	COEFFICIENT OF VARIATION PER CENT
1	5	7,360	±369	±485	±146	±6.6
	5	*8,466*	*±508*	*±597*	*±180*	*±7.0*
2	5	4,194	±233	±245	±74	±5.8
	5	*5,072*	*±495*	*±600*	*±181*	*±11.8*
3	5	8,467	±661	±744	±224	±8.8
	5	*11,041*	*±1817*	*±2090*	*±628*	*±18.9*
4	5	4,118	±159	±189	±57	±4.6
	5	*5,117*	*±227*	*±395*	*±119*	*±7.6*
5	5	5,130	±472	±584	±176	±11.4
	5	*5,456*	*±360*	*±371*	*±112*	*±5.7*
6	5	6,427	±293	±320	±97	±5.0
	5	*8,564*	*±172*	*±180*	*±55*	*±2.1*
7	5	4,921	±383	±395	±119	±8.0
	5	*5,817*	*±792*	*±803*	*±241*	*±13.8*
8	5	5,286	±367	±425	±128	±8.1
	5	*6,622*	*±572*	*±609*	*±183*	*±9.2*
9	5	4,302	±199	±223	±67	±5.2
	5	*6,624*	*±504*	*±609*	*±183*	*±9.2*
10	5	6,293	±266	±292	±88	±4.6
	5	*8,845*	*±1135*	*±1236*	*±371*	*±13.9*
11	5	7,988	±656	±794	±239	±9.9
	5	*10,466*	*±439*	*±513*	*±154*	*±4.9*
12	5	5,407	±204	±261	±79	±4.8
	5	*6,048*	*±225*	*±299*	*±90*	*±4.9*
13	5	7,557	±246	±304	±92	±4.0
	5	*7,613*	*±318*	*±353*	*±106*	*±4.6*
14	5	4,407	±191	±219	±66	±4.9
	5	*5,691*	*±407*	*±504*	*±152*	*±8.9*
15	5	4,601	±212	±260	±79	±5.6
	5	*6,104*	*±273*	*±314*	*±95*	*±5.1*
Mean	5	5,764	±327	±383	±115	±6.5
	5	*7,170*	*±550*	*±627*	*±190*	*±8.5*

* The plain type numbers are the results from leucocyte counts taken under basal conditions, while the italic numbers are the results from counts taken during activity.

It will be noticed that while the mean leucocytic indices for the individual tended to be slightly higher during activity, the differences observed were not marked. The mean leucocytic index for the entire group under basal conditions was 14.7, while during activity it was 16.7. In only one individual, case 3, was the variation in the mean leucocytic index so great as to transfer the patient from the "slightly unfavorable" group under basal conditions to the "very unfavorable" group during activity.

DISCUSSION AND CONCLUSIONS

A study of leucocytic variations in tuberculous patients under basal and active conditions has been undertaken with careful regard for precise technical methods, particularly with reference to the errors in technique described by Ponder and coworkers (15).

The results confirm the findings of Ponder, *et al.* (15) and Jones and coworkers (19) in that the variations of the total leucocytic counts observed by these investigators are practically identical with the fluctuations detected in this study; the former group observed fluctuations not exceeding ± 8 per cent during activity, while the latter group detected variations of ± 9.4 per cent. The variations observed in this study were ± 6.5 per cent under basal conditions and ± 8.5 per cent during activity. Since the investigations of these workers were undertaken on normal individuals, the results of the studies in this paper suggest that the total leucocytic variations in tuberculous patients differ in no way, quantitatively, from those in normal persons, and that the mechanism of such fluctuations, whatever it be, is the same in both groups.

Precise comparison of our results with those of Medlar (14) and Kaminsky (13) is somewhat difficult not only because of differences in procedures used, but also because these workers did not present a statistical study of their findings, the need for which in such studies has been emphasized by Garry and Bryan (12). Nevertheless, we find our results at definite variance with those of Medlar and Kaminsky. Medlar observed that most of his subjects, whether in bed or at work, showed total leucocytic variations between 2,000 and 4,000. Similarly, Kaminsky found increases in the total leucocytic count, following brief mild activity, of 2,000 or over in 40 per cent of his patients. In only one instance did we find a fluctuation above 2,000 under basal conditions and in only three instances during activity. We attribute our smaller

leucocytic fluctuations to the technique used in determining the total leucocytic count, a description of which was given earlier in this paper.

The variations in the differential white cell counts do not support the findings of Kaminsky who detected striking variations in some of the cell types, with increases during activity greater than 100 per cent in some cases. The greatest coefficient of variation in the neutrophiles and lymphocytes, in our study, was about ± 14 per cent; none of the monocytic variations were of any import. Our figures indicate a somewhat greater fluctuation in the differential counts than found by Medlar who observed no variation greater than 7 per cent. It is not unlikely that the differences in our results, as compared to those of Medlar, were due to the error introduced by the distribution of the cells on the stained slide, a factor which Barnett (20) has described and emphasized as unavoidable. The striking fluctuations observed by Kaminsky may be explained in part by the inherent unavoidable error emphasized by Barnett and in part by the fact that Kaminsky counted only 200 cells in the differential determinations, whereas 400 cells should be counted for precise results.

We are in complete agreement with Medlar in his conclusion that the variations in the total and differential white counts do not materially affect the leucocytic indices; this is seen in our mean leucocytic indices which were 14.7 at rest and 16.7 during activity. At this point one might suggest that perhaps the constancy of our mean leucocytic indices is characteristic of the more favorable cases of tuberculosis, as were most of ours, and that perhaps less constant results would be found in the unfavorable groups; we answer this by referring to Medlar's work (14) in which unfavorable groups were studied with comparable constant results. It is indeed significant that, in spite of somewhat conflicting findings in the leucocytic variations, our final conclusions are in harmony with those of Medlar; this would tend to emphasize further the conclusion that the "physiological" leucocytic variations are of no essential importance in the final evaluation of the blood picture.

It is sufficient that the phthisiologist appreciates that leucocytic variations occur "physiologically," whether within the range observed by Medlar or by this author. However, it is imperative that he appreciates the need for precise technical methods in routine leucocytic counts on tuberculous patients, for only by such methods can the errors inherent in a technique be significantly reduced and the greatest value of the leucocytic picture be realized.

The author realizes that the group studied in this paper was too small

to permit a dogmatic conclusion; however, the technical precision with which these studies were carried out permits us to indulge in certain opinions which, collectively, lead us to agree with Medlar (14b) who stated: "The normal variations . . . . in the leucocytic picture do not invalidate the use of the leucocytic count in interpreting pathological processes in which the leucocytes participate."

SUMMARY

1. A study of leucocytic variations in tuberculous patients under basal and normal conditions of hospital life is presented.

2. Slight variations in the total leucocytic count are found both during a basal state and during activity; slightly greater variations are present in the differential counts, but these are not striking.

3. These variations in the leucocytic picture do not alter the essential interpretation of the blood picture in tuberculosis.

4. The importance of precise technical methods in routine leucocyte counts is emphasized.

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REFERENCES

(1)(a) Webb, G. B., and Williams, W. W.: Colorado Med., 1909, *6*, 165.
(b) Webb, G. B.: Bull. Johns Hopkins Hosp., 1912, *23*, 231.
(2)(a) Murphy, J. B., and Ellis, A. W. M.: Jour. Exp. Med., 1914, *20*, 397.
(b) Murphy, J. B., and Sturm, E.: Ibid., 1919, *29*, 1.
(3)(a) Cunningham, R. S., Sabin, F. R., Sugiyama, S., and Kindwall, J. A.: Bull. Johns Hopkins Hosp., 1925, *37*, 231.
(b) Sabin, F. R., Doan, C. A., and Cunningham, R. S.: Tr. Nat. Tuberc. Assn., 1926, p. 252.
(4) Morriss, W. H., and Tan, S. H.: Amer. Rev. Tuberc., 1927, *16*, 729.
(5) Cunningham, R. S., and Tompkins, E. H.: Ibid., 1928, *17*, 204.
(6) Blackfan, K. D., and Diamond, L. K.: Amer. Jour. Dis. Child., 1929, *37*, 233.
(7) Flinn, J. W.: Ann. Int. Med., 1929, *2*, 622.
(8) Medlar, E. M.: (a) Amer. Jour. Path., 1926, *2*, 275.
(b) Amer. Rev. Tuberc., 1929, *20*, 312.
(9) Medlar, E. M.: Amer. Rev. Tuberc., 1929, *20*, 312.
(10) Griesbach, R.: Ztschr. f. Tuberk., 1930, *56*, 177. (Quoted by Medlar, E. M.: Amer. Rev. Tuberc., 1931, *23*, 389.)
(11) Wiseman, B. K., and Doan, C. A.: Amer. Rev. Tuberc., 1934, *30*, 33.
(12) Garry, W. E., and Bryan, W. R.: Physiol. Rev., 1935, *15*, 597.
(13) Kaminsky, J.: (a) Amer. Jour. Med. Sc., 1933, *186*, 484.
(b) Amer. Rev. Tuberc., 1935, *31*, 480.
(14) Medlar, E. M.: (a) Amer. Rev. Tuberc., 1929, *20*, 313.
(b) Arch. Int. Med., 1936, *57*, 367.

(15) PONDER, E., SASLOW, G., AND SCHWEITZER, M.: Quart. Jour. Exp. Physiol., 1931, *21*, 21.
(16) TIGERSTEDT, R.: Handbuch der Physiologischen Methodik, S. Herzel, Leipzig, 1913, B: 11 2, part 2, p. 11.
(17) MEDLAR, E. M.: Amer. Rev. Tuberc., 1929, *20*, 312.
(18) DAVENPORT, C. B., AND EKAS, M. P.: Statistical methods in biology, medicine and psychology, John Wiley and Sons, Inc., New York, 1936, ed. 4.
(19) JONES, E., STEPHENS, D. J., TODD, H., AND LAWRENCE, J. S.: Amer. Jour. Physiol., 1933, *105*, 547.
(20) BARNETT, C. W.: Jour. Clin. Invest., 1933, *12*, 77.

RESULTS OF INTENSIVE STUDY OF SPUTUM IN PULMONARY TUBERCULOSIS[1,2]

HENRY STUART WILLIS AND RUBY G. KELLY

In this day of modern treatment of tuberculosis when close attention is given to sanatorium regimen and surgical indication, patients are observed for change in weight or sense of fatigue, for alteration in local signs and symptoms and, fortunately, for roentgenological change. But how often adequate examination of the sputum is neglected! The tubercle bacillus stands in direct aetiological relationship to tuberculosis and has been known longer than many other pathogenic bacteria. Think of disregarding diphtheria bacilli in a throat culture or smear! How we search the stool, urine and blood for typhoid bacilli in the person suspected of harboring it either as a victim or carrier! Yet in tuberculosis where infection is rarely immediate and where the incubation period may be long, the epidemiological and often the diagnostic significance of disclosing the bacillus is overlooked. Everyone knows the value of uncovering tubercle bacilli as a diagnostic manoeuvre of first water, as a guide or measure of adequate treatment and as a sanitary or public health attack upon a disease that is always current in every community. Yet we pay too scant attention to an aetiological agent that is responsible for the spread of this still major disease.

Does our relative lethargy in this respect—our sense of the relative unimportance of the tubercle bacillus—come from our knowledge that tuberculosis is preëminently a disease of remissions and recessions and that its status is frequently changing? Whatever the cause, it does seem logical to demand that good routine tuberculosis practice should search carefully, at frequent intervals and by various means, for the agent that causes "every case to come from another."

When is the sputum negative? And what is a negative sputum? These are questions that have demanded increasing attention in recent

[1] Presented at a session of the 33rd annual meeting of the American Sanatorium Association, Los Angeles, California, June 20, 1938.

[2] From the Wm. H. Maybury Sanatorium (Detroit Municipal Tuberculosis Sanatorium), Northville, Michigan.

years. Pinner and Werner (1) made the issue acute in 1928 when they demonstrated tubercle bacilli in more than 99 per cent of 507 cases of active pulmonary tuberculosis by employing various techniques suitable to the circumstances. More recently Pinner (2, 3) has emphasized the definite value of negative sputum examinations, the need of proper collection of sputum even over a period of several days, and has challenged the phthisiologist to measure the efficiency of collapse procedures by adequate examinations of the sputum.

In this time-worn question of sputum examination, emphasis has been placed over and over again upon the proper collection of specimens, the proper technique in selection and preparation of the parts to be studied, the evaluation of the various accepted methods of examination, the relative merits of methods, such as that of concentration, culture and guinea-pig inoculation. These are now well established and too well known to rate discussion at this time. It is not a question of methods but the application of methods and the clinical use and appraisal of them that appear at fault.

At Maybury Sanatorium we have endeavored to screen the sputum carefully from the standpoint of (*1*) its value as a guide to and indication for treatment, (*2*) its helpfulness in prognosis, and (*3*) its use in gauging the adequacy of collapse manoeuvres. In addition, efforts were made to ascertain what types of sputum examination offer the best and most reliable results. To these ends we began in June, 1935, to make intensive examinations of the sputum of patients who had been negative by direct smear and concentration (and in one series by culture) for at least six months. The method consisted in the collection and pooling of the total daily production of sputum for two consecutive seven-day periods. This yielded two weeks' total sputum in two pooled specimens. Each of these was concentrated by hydrochloric acid and examined microscopically: if negative, the entire residue left after concentration was divided equally for cultural studies and guinea-pig inoculation. Cultures were examined biweekly for twelve weeks. Records were kept of the positive and negative condition of the sputum prior to the fourteen-day study. Both the Loewenstein and the Petragagni media were used.

A few circumstances will arise in which all the proposed features of the seven-day specimen scheme cannot be carried out feasibly, as, for instance, in the patient with a large volume of sputum. We have determined that the optional volume of the pooled specimen is 50 cc. or less. More than 50 cc. can be used, but the results appear to be not quite as reliable. Exact data are not available on this point. Experi-

ence has shown that the average negative case produces relatively small amounts of sputum (less than 50 cc. in a week), except for the rather rare case who has developed bronchiectasis in the wake of his tuberculosis. In the work reported the entire volume of sputum has been concentrated, flasks being used where necessary. In some instances we have used four, in some six tubes. At no time have all the tubes been contaminated; in fact an occasional contaminant is a rarity. Of 600

TABLE 1*

Comparison between sputum findings and clinical course

	TOTAL CASES	CONDITION 6 MONTHS TO 3 YEARS AFTER DISCHARGE							
		In hospital		Same or better		Worse		Dead	
		Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent
Negative 14 days—previously negative.	52	6	11.5	42	80.8	3	5.8	1	1.9
Negative 14 days—previously positive.	81	4	4.9	72	89.0	3	3.7	2	2.4
Positive 14 days—previously negative..	28	9	32.1	16	57.2	0		3	10.7
Positive 14 days—previously positive..	94	23	24.5	59	62.8	5	5.3	7	7.4
Negative 14 days.....	133	10	7.5	114	85.6	6	4.6	3	2.3
Positive 14 days.....	122	32	26.2	75	61.5	5	4.1	10	8.2
Total.....	255†	42		189		11		13	

*The data shown in this table are not classified as to the time elapsed between "previously positive" and the 14-day examination. For instance, of the 175 previously positive cases 94, or 54 per cent, were positive on 14-day examination. However, a minimum of 6 months had always elapsed and often as long as 3 years had elapsed between the last "previously positive" examination and the 14-day examination. Nearly all the 14-day examinations were done on patients deemed about ready for discharge. The "previously positive" examinations represented positives on any examination whether by direct smear, concentration, culture or guinea-pig inoculation and are therefore not exactly comparable to the 14-day examination.

† At the time of compiling these data, follow-up records were available on only 255 of the original 300 patients shown in other of the tables. Since then 37 others have been contacted. However, the additional data do not change the percentages materially.

specimens, only one showed contamination in all tubes. Of all tubes used, 10 per cent were contaminated.

So much for technique. Insofar as we could, we disregarded the results of the fourteen-day study when discharge was considered or when the question of collapse presented itself, in order that a true prognostic evaluation might be obtained. Patients were followed from six months to three years after discharge and were classified, as shown in table 1, as being in the same or better condition, still in the hospital,

worse, or dead, and these listed for the fourteen-day negative and the fourteen-day positive groups. The large number of patients listed under the fourteen-day negative heading may be explained by the fact that these cultures were done a comparatively short time before discharge, the average being about six months even when the periodic, repeated tests on long standing cases were included. It will be seen that, among the positives, more than three times as many remain in the hospital, 25 per cent fewer are in the group of "same or better," about the same number are worse and four times as many are dead. So it appears that fourteen-day positive sputum examinations indicate a poorer prognosis than fourteen-day negative examinations do.

Table 2 reveals what one might expect to be true in that a much larger percentage of minimal cases are listed in the negative fourteen-day group and a much larger percentage of far advanced cases fall in the positive fourteen-day group.

TABLE 2

Sputum findings according to stages of the disease

	CHILDHOOD TYPE	MINIMAL	MODERATELY ADVANCED	FAR ADVANCED
	per cent	*per cent*	*per cent*	*per cent*
Negative 14 days	6.32	31.01	32.53	29.97
Positive 14 days	8.45	10.56	36.62	44.36

From the prognostic import of this scheme as indicated in table 1, it follows that such detailed examination of the sputum might be a reliable and helpful guide to treatment; might be usefully employed as an index to the need of change in treatment, especially the addition of collapse therapy; could be helpful in really determining whether a case is active.

Careful sputum observation is highly important when applied periodically after collapse, as a gauge of the efficiency of the collapse procedure. We are making an effort to apply the pooled sputum technique to patients at six, twelve and eighteen or more months after phrenic operation, pneumothorax, thoracoplasty or any other collapse procedure. At present the data show that such a scheme is helpful in indicating whether the procedure has been successful in converting the sputum, but they are not yet complete enough to justify detailed presentation.

The laboratory work required to carry on a program of fourteen-day sputum examinations is considerable, and questions arise as to the

practical application of this scheme in a more or less routine way. Is it feasible to carry out such studies from time to time on all cases that are negative by other means? If not, will less than a fourteen-day specimen yield comparable results? To answer this question we have tabulated these results in respect to the two consecutive total seven-day specimens which made up the total fourteen-day specimens, with the results shown in table 3. Of specimens from 300 consecutive patients, 47 instances occurred in which one seven-day collection was positive and the other negative. If only one seven-day collection had been made, instead of two, 23, or one-half of this discrepancy, could be reckoned as showing negative results. This means that one seven-day collection of sputum would fail by 7.8 per cent to yield as many positive results as the fourteen-day specimen. Considering the relatively slight increase in efficiency of the fourteen-day concentrate over the seven-day concentrate, it seems reasonable to save the laboratory the increased burden involved in running the second seven-day concentrate.

TABLE 3

Comparison of efficiency of different methods of sputum examination

TOTAL SPECIMENS	ONE 7-DAY NEGATIVE, ONE 7-DAY POSITIVE	GUINEA PIG POSITIVE, CULTURE NEGATIVE	GUINEA PIG NEGATIVE, CULTURE POSITIVE
300	47	33	17

The efficacy of the pooled specimen was studied in still another way. The total production of sputum was collected daily for eleven days: that collected on the sixth day was not added to the total but was concentrated and cultured separately. The pooled specimen, composed of the total collection of the remaining ten days of the eleven-day period, was concentrated and cultured and the results of these two sets of cultures—one a twenty-four-hour and one a ten-day culture—compared. The results appear in table 4. Eighty patients furnished sputum, from which 38 cultures, 47.5 per cent, showed growth. Of these the one-day specimens were positive 24 times (63.1 per cent of all positive cultures) and the ten-day specimens 35 times (92.1 per cent of all positive cultures). From this it appears that the ten-day culture has an efficiency of 92.1 per cent against that of 63.1 per cent for the twenty-four-hour specimen. This indicates the superior efficiency of the multiple day concentrate over the single day concentrate. We have made no comparison between the ten- and seven-day concentrates but we believe that the seven-day

concentrate is a good working compromise. These 80 patients were negative on concentration.

Another interesting fact disclosed by table 3 is that of the relative efficiency of culture and guinea-pig inoculation. Among 300 specimens the results of guinea-pig inoculation were positive 33 times when the cultures made from the same specimens were negative, and culture was positive 17 times when the guinea pig was negative. However, in 10 of the 17 instances, the guinea pigs died before observations were completed, and this fact illustrates one of the disadvantages of the guinea-

TABLE 4

Comparison of culture of one-day and ten-day pooled sputum

Total patients	80
Total cultures showing growth	38
Positive one-day culture	24 —63.1% of all positive cultures
Positive ten-day culture	35*—92.1% of all positive cultures

Efficiency of the ten-day culture is 92.1% against that of the one-day culture which is 63.1%.

* Three specimens appearing positive in one-day culture were negative in ten-day culture.

TABLE 5

Comparative effectiveness of microscopic examination, culture and animal inoculation

	TOTAL NUMBER	NUMBER POSITIVE	PER CENT POSITIVE
Smear	408*	17	4.1
Culture	408	135	33.1
Guinea pig inoculations	408	153	37.5

* The figure of 408 shown in this table represents the addition of 108 patients to the 300 as presented in other parts of the paper.

pig method. If guinea pigs are to be used, it seems desirable to inoculate two animals with each specimen.

It may be stated also in this connection that, in recent years, because of improvements in technique and in media, the incidence of positive cultures in otherwise negative specimens has increased steadily. In 1928 culture yielded tubercle bacilli in 21 per cent more specimens than did concentration and microscopical examination. In 1934 this incidence was 29 per cent and in 1937 cultures revealed bacilli in 34 per cent more cases than concentration and microscopical examinations did.

In this connection also the data disclosed in table 5 are germane. This table shows the results of examination by microscope, culture and

guinea-pig inoculation of the multiple concentrate (fourteen-day) of 408 patients who had been negative by other methods for six months or longer. The "other methods" referred to include culture of twenty-four-hour specimens in about one-third of the cases. The data indicate that microscopical examination of sputum in these cases that were negative for long periods revealed tubercle bacilli in 4 per cent; that culture proved their presence in 33 per cent and guinea-pig inoculation in 37 per cent

DISCUSSION

These facts have caused us to lean heavily upon this type of sputum examination which, by way of restatement, consists of (*1*) the daily collection of all sputum produced for seven consecutive days; (*2*) pooling of these specimens and concentration of the total volume; (*3*) microscopical examination of the concentrate; (*4*) if the latter is negative, culture of the total residue of the specimen upon at least six culture tubes. The inoculation of guinea pigs yields a somewhat higher incidence but has a few drawbacks and is optional in our laboratory. Such studies done on "negative" cases shortly after admission and at intervals thereafter, and especially at regular periods after collapse has been instituted, offer a basis for judging progress and act as a guide to management. If some such scheme could be adopted by sanatoria in general, our terms of "negative" and "positive" would have strict definition and would be comparable.

We suggest the adoption of the seven-day concentrate with culture as a standard for determining, in a practical way, the presence or absence of tubercle bacilli in the sputum. The practical aspects of this scheme as a "standard" may be justified on several counts. It requires but little more time, effort and equipment than ordinary concentration of a single or a 24-hour specimen; technically it is neither more difficult nor complicated than study of equal magnitude on smaller amounts of sputum; it is definitely more efficient in detecting tubercle bacilli than similar examination of single or twenty-four-hour specimens; it yields data of at least moderate prognostic value.

We see two possible objections to this scheme of sputum analysis. One is the delay of several days in delivery of the sputum report, especially in the newly admitted case. This can be obviated readily by performing the customary initial examinations and, if these are negative, following soon thereafter with the seven-day examination. The other

objection rests in the question of how detailed sputum examination need be. Many physicians hold that the presence of tubercle bacilli in the sputum is of relative insignificance. To them, a scheme of careful search for tubercle bacilli is unnecessarily meticulous and may lead to loss of perspective. In such argument one can merely invoke common sense and the trite statement that the tubercle bacillus, after all, is the *conditio sine qua non* of tuberculosis; that tubercle bacilli in the sputum constitute a threat to their possessor and to his family and his friends; that positive sputum indicates poorer prognosis than negative sputum; that the natural tendency in improving cases is toward negative sputum; that the opportunity for exacerbation or spread is definitely greater in the person who produces tubercle bacilli in his sputum.

In striving for the ideal, one is often confronted with practical difficulties. In diagnosis (and in management of patients) one should be able to attain the ideal of identifying the occasional single bacillus in the patient's sputum. When the question of discharging the patient arises, one must face the practical impossibility of keeping every patient in the hospital until the day when all cultural studies of his sputum are completely negative. From the practical point of view one must recognize that, in many patients, an occasional positive sputum culture is compatible with health. Under the circumscribed regimen of a guarded life, many such patients may adjust their domestic circumstances, activities and work so that the potential danger to patient and associates will be negligible—this despite the fact that ultimate prognosis is less favorable in such people than in their always-negative fellow patients.

SUMMARY

1. Need is had for sharper definition of "negative" and "positive" sputum in patients with pulmonary tuberculosis.

2. Collection, concentration and culture of at least a week's total sputum is helpful as a means of diagnosis, as a guide to the care and an aid in prognosis of the case of pulmonary tuberculosis whose sputum has been negative by the usual techniques employed.

3. This type of study is offered as a standard for evaluating the results of sputum examinations.

REFERENCES

(1) PINNER, M., AND WERNER, W. I.: The significance of positive and negative sputum findings in pulmonary tuberculosis, Amer. Rev. Tuberc., 1928, *18*, 490.

(2) PINNER, M.: Sputum examination in pulmonary tuberculosis, Jour. Lab. & Clin. Med., 1932, *17*, 611.

(3) PINNER, M.: Negative sputum, Jour. Thoracic Surg., 1936, *5*, 476.

TUBERCLE BACILLI IN SPUTUM[1,2,3]

Criteria for Negativity, and the Significance of the Number of Bacilli Found

EMIL BOGEN AND EDWIN S. BENNETT

Sputum examinations are performed, not only to determine whether the patient has tuberculosis, but also to reveal activity, and in a measure the degree of infectivity, or the extent of healing of the lesion. Sputum examinations are both qualitative and quantitative. Quantitative reports are of interest and value as an aid in prognosis, the therapeutic and public health management, and the evaluation of results of treatment. A qualitative report establishes the diagnosis, as it makes little difference whether the positive report means one or one million microorganisms, whether the slide is loaded or the guinea pig is barely infected, so long as it is positive. It is in the management of proved cases that these distinctions become important.

The Gaffky count (1), based upon the number of acid-fast bacilli seen per oil immersion field on a simple direct smear of the sputum, usually taken from the first morning specimen, is the most widely used measure of the abundance of microörganisms in the sputum, and is of considerable clinical and prognostic importance (2).

The area of the oil immersion field used in counting bacilli on a smear varies somewhat with the oculars and objectives used and the tube length, but is generally not far from 0.015 square millimetres, giving about 6,666 such fields per square centimetre of slide surface. The depth of the material spread on a slide varies, depending on the consistency of the specimen and the size of the loop, as well as the area covered, but in an ordinarily thick smear is about 20μ or .02 mm. The number of bacilli contained per cc. then would be about 50 times the number seen per square centimetre, or about 333,000 times the number seen per

[1] Presented at a session of the Pathological Section at the 34th annual meeting of the National Tuberculosis Association, Los Angeles, California, June 22, 1938.

[2] From the Olive View Sanatorium, Olive View, California.

[3] This study was made with the aid of the Laennec Society of San Francisco, the Trudeau Society of Los Angeles, the laboratory staff of Olive View Sanatorium and the Works Progress Administration Project No. 465-03-3-178, to all of whom thanks are hereby rendered.

field. Since a careful worker will examine 300 fields before reporting a smear as negative, it would appear that as few as 1,000 separate bacilli per cc. might be revealed by careful microscopical examination of the sputum considerably below the oft cited figure of 100,000 given as the lower limit by Corper (3).

If the direct smear were made at random by mixing the specimen and then taking several successive loopfuls from different portions for

TABLE 1

GAFFKY COUNT	NUMBER PER FIELD	NUMBER PER CC.
I	0.003	1,000
II	0.1	33,000
III	1.0	350,000
IV	2.0	660,000
V	4.0	1,350,000
VI	7.0	2,350,000
VII	15.0	5,000,000
VIII	30.0	10,000,000
IX	100.0	33,000,000
X	300.0	100,000,000

TABLE 2

Effect of homogenizing

Frequency of findings in 100 paired counts

NUMBER OF BACILLI PER 100 FIELDS	SELECTED PARTICLE	HOMOGENIZED DILUTION
1,000	15	9
100	39	30
10	7	14
1	4	5
0	35	42

the smear, the Gaffky count might be taken as an index to the total concentration of the bacilli in the specimens (4). This, if multiplied by the volume of the specimen in twenty-four hours might, therefore, indicate the daily bacillary output. Actually, however, the direct smears usually are not made from a random sample, but from particularly suspicious particles. These yield a higher percentage of positive findings than would be found by random sampling, and consequently a much higher count (5). With the introduction of antiformin and other digestants, and the use of incubation and shaking it is possible to produce

a more homogeneous dispersion of the bacilli in the sputum (6). The number of bacilli found per unit volume of such suspensions makes possible an estimation of the total number of bacilli in the entire specimen. This gives a quantitative measure of the rate of excretion, more reliable as well as more complete than the figure obtained by the Gaffky count on the simple direct smear.

TABLE 3

Centrifuging versus flotation

Frequency of findings in 100 paired counts

NUMBER OF BACILLI PER 100 FIELDS	SEDIMENT	SUPERNATANT
1,000	45	39
100	25	27
10	10	9
1	6	11
0	14	13

TABLE 4

Effect of counterstain

Frequency of findings in 100 paired counts

NUMBER OF BACILLI PER 100 FIELDS	METHYLENE-BLUE	PICRIC ACID
1,000	42	43
100	28	24
10	9	9
1	8	11
0	13	13

The method of concentration, either by centrifuging at high speed and examining the sediment or by the addition of water-immiscible materials to which the tubercle bacilli will adhere, makes possible the collection of the bacilli present in the specimen in but a fraction of their original volume. Experiments performed recently at Olive View Sanatorium indicate that, although neither sedimentation nor flotation may remove all of the bacilli from heavily laden material, they do ordinarily concentrate in the final small volume the greater part of the original bacillary content.

In a series of 100 admission specimens studied comparatively at Olive View, we have not been able to find any greater number of bacilli by flotation than by sedimentation; nor has the picric acid counterstain

given us any more bacilli than the dilute methylene-blue counterstain used in the Ziehl-Neelsen technique. The flotation technique does have the advantage that, since it contains less debris, it is possible to superimpose repeated layers of material on the same area, in which a much higher yield might be expected. On the other hand, the agents used for flotation are destructive to the bacilli, making it impossible to make cultures or animal inoculations from the same material, and we have found false positive results more often with the use of flotation.

TABLE 5

Variation in 200 paired counts

NUMBER OF BACILLI PER 100 FIELDS METHYLENE-BLUE SLIDE	NUMBER OF BACILLI PER 100 FIELDS PICRIC ACID SLIDE					
	0	1	10	100	1,000	Total
1,000	0	0	0	3	56	59
100	1	0	2	31	4	38
10	3	3	9	0	0	15
1	3	8	1	0	0	12
0	72	3	1	0	0	76
Total.....	79	14	13	34	60	200

TABLE 6

Centrifuging versus flotation on 300 specimens

SEDIMENT NUMBER OF BACILLI PER 24 HOURS	SUPERNATANT NUMBER BACILLI PER 24 HOURS					
	0	10,000	100,000	1,000,000	10,000,000	Total
10,000,000	0	0	1	10	68	79
1,000,000	0	3	3	36	9	51
100,000	5	5	11	5	1	27
10,000	3	7	2	1	0	13
0	114	8	4	4	0	130
Total.....	122	23	21	56	78	300

Where the tubercle bacilli in the specimen are extremely few, numbering less than 1,000 per cc. or clumped so that they are irregularly distributed, microscopical examination usually fails to reveal them and we must resort to cultural methods and animal inoculation.

The quantitative method for sputum examination used at Olive View is as follows:

1: Collect entire 24-hour sputum specimen in a clean wide-mouthed glass jar.
2: Add an equal volume of 4 per cent sodium hydroxide. Close tightly and shake in mechanical shaker for 30 minutes.
3: Add a drop of phenol red indicator solution, and neutralize with 10 per cent hydrochloric acid.
4: Pour into large sized centrifuge tubes graduated at 1 cc., and centrifuge for 15 minutes at about 2,000 r.p.m.
5: Remove supernatant liquid, leaving 1 cc. sediment. Mix sediment and take up 0.1 cc. in a marked, clean, capillary pipette with rubber bulb.
6: Smear out evenly over a 5-square centimetre area on a glass slide.
7: Stain with steaming carbolfuchsin for 5 minutes.
8: Decolorize with 20 per cent sulphuric acid for about 10 seconds and then with 95 per cent alcohol for about 15 minutes.
9: Counterstain with 1:50 dilution of Löffler's methylene-blue.

The average number of bacilli found per field, divided by 3, gives the approximate number of million tubercle bacilli per day.

The figure calculated as the probable daily number of tubercle bacilli excreted is not accurate. It is subject to the following errors:

1: Swallowing or other loss of bacilli
2: Inadequacy of digestion or homogenization with consequent clumping and undercounting, or destruction of the bacilli in the process so that they do not take the stain
3: Unequal distribution on the smear and irregularity of staining
4: Sampling errors in the actual count made, particularly in the failure to count the number of individual bacilli in clumps

Nevertheless the counts obtained do represent a probable minimum figure for the total excretion. The error is generally not sufficiently great to invalidate conclusions drawn from these figures. Consequently marked variation in the excretion of tubercle bacilli may be of interest and value, both in the study of the individual and in the review of a series of cases.

A few of the checks which cause us to lend credence to those figures are as follows:

1: Two hundred paired counts were made with different 0.1 cc. samples of the same sediment or flotation specimen. The average number of bacilli seen per field showed less than 10 per cent differences between pairs of slides.

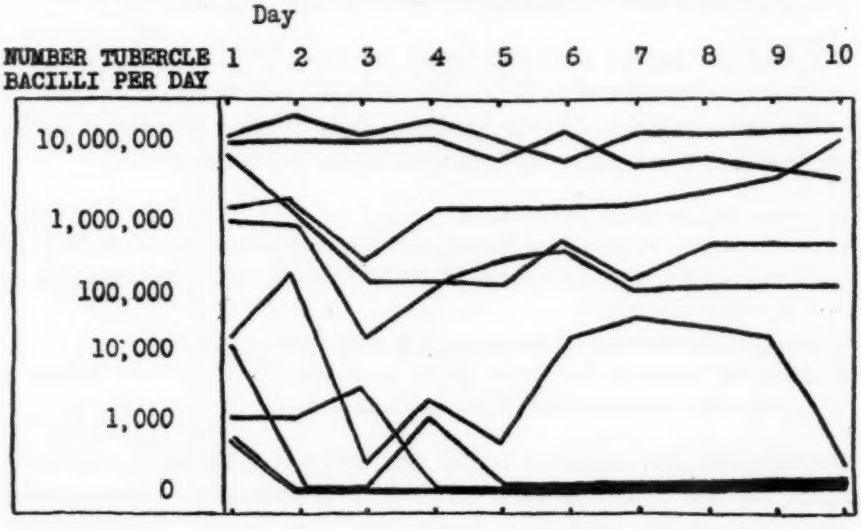
2: In 300 specimens studied by a dilution-flotation technique, using xylol, as compared with the centrifuging technique, treating the two halves of each specimen after initial homogenization in entirely different manner, the counts varied fairly consistently in the same direction.

3: Daily counts of the number of tubercle bacilli excreted by the same patient on successive days for periods of a week or more showed figures generally of the same magnitude.

4: Parallel cultures and guinea-pig inoculations made on specimens positive on concentration show, in general, increasing amounts of colonies or lesions with increased number of bacilli found on the slide.

TABLE 7

Daily variations in bacillary output, Olive View, 1938, 10 patients during 10 days



The number of bacilli excreted in the sputum is related to the type and extent of the diseased process in the lungs. Patients with soft excavating lesions may expectorate many millions of bacilli during the period of excavation (7), while old fibrotic cavities may yield a fairly constant medium number for a long time.

In our wards with the sicker patients having intestinal, laryngeal and ulcerative tracheobronchial tuberculosis, not only is the percentage of positive sputum very high, but the number of bacilli expectorated per day generally runs in the millions. In patients under collapse therapy this number rapidly diminishes. In our ambulatory wards positive sputum is uncommon, and, when found, usually shows only

such small numbers of bacilli as to require concentration, culture or guinea pigs for their detection.

The relationship of sputum findings to prognosis is illustrated in the records of nearly 10,000 admissions to Olive View Sanatorium during the past seventeen years. During this time the efficiency of the sputum examinations, their frequency and their delicacy have continually in-

TABLE 8

Culture and guinea pig

NUMBER COLONIES PER TUBE	NUMBER OF BACILLI PER DAY (FROM CONCENTRATION TEST)					
	0	1	1,000	100,000	10,000,000	Total
Too many to count	0	0	0	10	15	25
Over 10	0	4	4	5	7	20
1–9	0	8	2	3	0	13
0	59	9	0	3	3	74
AMOUNT OF LESIONS IN GUINEA PIG						
Large	0	9	0	11	22	42
Small	0	11	6	8	5	28
None	59	0	0	2	1	62

TABLE 9

Case fatality rates and sputum findings, all stages

SPUTUM RESULTS	NUMBER CASES	ANNUAL FATALITY RATE
Never positive	3,655	4.1
Negative on discharge	1,981	6.0
Positive on discharge:		
To culture or to guinea pig only	82	7.7
Rare on smear or positive on concentration only	1,238	27.7
Few on smear	1,688	34.1
Numerous on smear	1,008	48.6
Total	9,652	

creased, nevertheless the percentage of sputum conversions has greatly increased.

Reviewing the entire series, it is noted that most minimal cases were negative on admission, and remained that way. Most far advanced cases were positive at some time and the proportion who later became negative had gradually increased with the extended use of collapse therapy.

The mortality rate was noticeably higher in patients leaving the Sanatorium with strongly positive sputum.

In order to learn the attitudes of tuberculosis specialists, the following questions were sent to the members of two large tuberculosis medical societies on the West Coast:

1: What are your criteria of a negative sputum?
2: With reference only to sputum (and stomach washings) when do you allow:
(a) A child to go to school?
(b) A teacher to teach children in public school?
(c) A dentist to practice his profession?
(d) A husband and wife to live together without restrictions?
(e) A father or mother to return to a home which contains small children?
3: Once a sputum has become negative, according to your criteria, how often do you reëxamine it in the absence of obvious indications?

The 50 responses received show a wide divergence of opinions, but also a striking unanimity in regard to certain features. A distinction was often made between sensitivity of technique required as follows:

1: For diagnosis and treatment
2: Between institutional and private practice
3: Between the individual and the public health point of view

In general, it was held that for diagnosis, if clinical evidence was suggestive, the most searching methods, including guinea-pig inoculation, should be used, before the patient was dismissed as closed or nonclinically tuberculous. Even then a number of men emphasized the existence of active closed cases. For prognosis and treatment, although some workers are wary of even extremely rare bacilli, it was generally felt that the danger is much less with sputum negative to microscopical methods, even though a guinea pig might be positive. Several thought that the presence of a positive guinea pig alone was not sufficient to warrant further collapse therapy if the clinical course were otherwise favorable.

The public health significance of the sputum examination aroused the greatest difference of opinion. Some men held that a careful patient might be allowed considerable leeway despite strongly positive sputum. Others insisted on the isolation of all positive-sputum cases, however scanty the sputum or conscientious the patient. Where the daily output exceeds 1,000,000 acid-fast bacilli, the patient has a heavily laden spu-

tum, usually positive on simple smear and almost always on concentration. We believe that such a patient is dangerous both to himself and to others, and requires isolation and full precautions as regards contacts. Where the daily output lies between 10,000 and 1,000,000 bacilli, the patient has a clinically open case, sometimes positive on direct smear and usually so on concentration. Such patients require separation from children or intimate contacts, and the use of hygienic technique. Where the daily output is less than 1,000 bacilli, the patient has what is usually considered a clinically closed case, negative on most microscopical examinations, but often positive on culture or guinea-pig inoculation. Although the danger of spread from such a case is much less, and actual isolation may not be required, these patients should not only follow the sanatorium regimen and technique, but should have frequent sputum examinations to detect flare-ups with increase in output.

The use of sputum conversion as a guide to therapy constitutes one of its greatest values, both in the care of the individual case and in the evaluation of treatments given a series of patients. Only too often do we see accounts of an operation or other treatment reporting successful sputum conversion on only the most superficial and cursory examinations. Obviously this cannot be compared to the findings with more delicate measures.

The knowledge of the method used for the original finding of positives, as well as for the later negative findings, is essential for the correct evaluation of sputum conversion. *The technique following the treatment should be at least as sensitive as that which yielded the previous positive finding before a patient should be recorded as having had sputum conversion.* The number of negative reports following treatment should be substantially greater than the number of such negative reports previous to treatment before conversion may be accepted.

CONCLUSIONS

Adequate sputum examination requires repeated representative specimens, properly collected over a long enough time period. They must be examined by a delicate method, such as selection, concentration, or flotation; and carefully stained for a sufficient time to disclose a few thousand bacilli per cc.; or by culture or animal inoculation capable of revealing a few viable bacilli in the daily output. The method used and the approximate number of tubercle bacilli found should be reported.

Phthisiologists ought to refrain from claiming sputum conversion in

reporting the results of methods of therapy without using due caution in determining that there actually has been a change from positive to negative. Quantitative aspects of sputum examination should not be neglected if we are best to serve the individual patient, safeguard the public and properly evaluate our therapeutic measures.

REFERENCES

(1) GAFFKY: Ein Beitrag zum Verhalten der Tuberkelbacillen im Sputum, Mitth. aus dem Kaiserl. Gesundheitsamte, 1884, *2*, 126.

(2) HEISE, F. H.: Prognosis in tuberculosis from the standpoint of the occurrence of hemoptysis and tubercle bacilli in the sputum, Amer. Rev. Tuberc., 1917, *1*, 280.

(3) CORPER, H.: Certified diagnosis of tuberculosis, Jour. Amer. Med. Assn., 1928, *91*, 371.

(4) POTTENGER, J. E.: Laboratory methods, in vol. I, p. 533 of POTTENGER, F. M.: Clinical tuberculosis, ed. 2., 1928.

(5) MISHULOW, L., MELMAN, M., AND ROMANO, M.: An improved method of direct smear examination for acid-fast bacilli in sputum, Science, 1934, *80*, 143.

(6) ELLERMAN AND ERLANDSEN: Nachweis von Tuberkelbazillen im Sputum, Ztschr. f. Hyg., 1908, *61*, 219.

(7) LONG, E.: From pathology to epidemiology, Jour. Amer. Med. Assn., 1935, *104*, 1883.

(8) PINNER, M., AND WOOLLEY, M. T.: Negative sputum, Jour. Thoracic Surg., 1936, *5*, 476.

PATHOLOGY AND PATHOGENESIS OF PULMONARY ARTERIAL ANEURYSM IN TUBERCULOUS CAVITIES[1,2]

OSCAR AUERBACH

Although Laennec (1) discussed the possibility of an aneurysm of the pulmonary artery as a source of haemoptysis as early as 1827, the first actual observation of this type of aneurysm, later designated the "Rasmussen aneurysm" and renamed "erosion aneurysm" by Eppinger (2), was not made until 1841, by Fearn (3).

Between 1841 and 1900, detailed studies of pulmonary arterial aneurysm were made by several authors, notably Menetrier (4), Meyer (5), and Eppinger (2). Menetrier reported an incidence of two per cent in 1899.

Since 1900 very little has appeared in medical literature regarding pulmonary aneurysm, despite the extension of our knowledge of tuberculosis in general. For this reason we believe it of interest to report our experience concerning incidence and our findings as to aetiology and pathogenesis of pulmonary arterial aneurysm as noted in patients who have died of pulmonary tuberculosis at Sea View Hospital.

In a consecutive series of 1,114 autopsies of chronic pulmonary tuberculosis with cavitation, we have noted 45 cases of pulmonary aneurysm, an incidence of 4 per cent. In 1933 Pagel (6) reported an incidence of 5 per cent.

In 38 of our 45 patients with aneurysm, the aneurysm ruptured and was the immediate cause of death. Of the remainder, 5 had from one to many haemorrhages from one day to two months before death and death resulted either from exsanguination or from the dissemination of tubercle bacilli and consequent spread of the tuberculous process from the cavities via the bronchi to other parts of the lung. The aneurysms in the other two were intact and were an incidental finding at autopsy.

It is not unusual for an individual to give a history of having had one or

[1] Presented at a session of the Pathological Section at the 34th annual meeting of the National Tuberculosis Association, Los Angeles, California, June 22, 1938.

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more severe haemorrhages long after the onset of pulmonary tuberculosis and before fatal haemoptysis. Yet diligent search at autopsy fails to reveal any source of the previous bleedings other than aneurysmatic dilatation of the pulmonary artery. It is possible that the previous haemorrhages were caused by rupture of the pulmonary aneurysm, but instead of proving fatal one of two possibilities occurred. One possibility is that blood within the cavity clotted and formed a tamponade, thus terminating what might otherwise have been fatal bleeding. With shrinkage of the clot, the tamponade effect is lost and another haemorrhage occurs. Such a sequence of events would account for the repeated large haemorrhages that so frequenty occur during the few days immediately preceding fatal haemorrhage. Another possibility is that the fibrin of the clotted blood fuses with the fibrin of the wall of the aneurysm and so reinforces it that months pass before the wall of the aneurysm is again unable to resist the pressure within the pulmonary vessel and rupture recurs. Rasmussen (7) has explained haemorrhage preceding fatal haemorrhage as being due to very small openings in the aneurysm through which the blood makes its way into the cavity where it coagulates and remains until a fresh spell of coughing loosens the coagulum and brings about further haemorrhage.

Age incidence: Aneurysm of the pulmonary artery may be observed at any age in which the ulcerative form of pulmonary tuberculosis is seen, but the incidence in general conforms to the age period in which pulmonary tuberculosis is most frequently encountered, namely, in the third and fourth decades. The youngest case reported is that of Powell (8), who found a ruptured pulmonary aneurysm in a seven months old child. Twenty-nine of our 45 cases were between the ages of twenty and forty years. The youngest was twenty and the oldest sixty-five years of age.

Sex and race incidence: Thirty-three of the patients with aneurysm were males and 12 were females, corresponding to the ratio of male to female autopsies at Sea View Hospital.

Thirty-four of the patients were white and 11 colored, an interesting proportion in view of the fact that the autopsy incidence at Sea View Hospital is 5 white to 3 colored patients. The lower incidence of aneurysm in colored patients in contrast to the percentage of colored patients coming to autopsy raises the question as to whether there is a difference in the type of pulmonary tuberculosis that develops in the Negro. It is claimed (Pinner and Kasper (9)) that pulmonary tuber-

culosis in the Negro is of a more exudative nature and manifests chronic changes less frequently than pulmonary tuberculosis in the white race. The latter factor in particular may have a bearing on the lower incidence of aneurysm in the colored race for the reason that, as already shown by Rasmussen (7), Powell (8), Fraentzel (10), Eppinger (2) and Bogen (11), aneurysm develops in chronic cavities.

Site: The pulmonary aneurysm was found in the left lung in 26 cases, and in 20 of these it was present in the left upper lobe. It occurred in the right lung in 19 patients. Bogen (11), who reported 43 cases having pulmonary haemorrhage during their stay in the hospital, found the source of bleeding at autopsy to be twice as common from the left as from the right lung.

Number of aneurysms: Some authors, notably Letulle (12) and Rasmussen (7), have found multiple aneurysms, but the majority of those reported have been single. Letulle noted two dilatations in one patient, and Rasmussen two in one, and four in another case. In every instance of the Sea View Hospital series a single aneurysm was present.

Gross appearance: In all of our cases the aneurysm was found within a chronic excavation, the size of which bore no relation to that of the dilated vessel. The cavity wall was thick and protruding from its inner surface, usually in the medial aspect, was the aneurysm of a branch of the pulmonary artery. In nearly every instance the vessel was collapsed and obscured by the clotted blood that completely filled the cavity lumen, becoming clearly visible only after the blood had been gently washed out of the cavity. The fact that aneurysms are extremely friable and may easily be washed away or detached as the blood clots are being removed with instruments may account for the failure to find the source of bleeding in many cases of fatal haemorrhage.

Although aneurysms occasionally develop in trabeculae which traverse tuberculous cavities, the great majority of aneurysms develop in arteries which lie outside the cavity and approach the excavation tangentially. The trabeculae represent the blood vessels present within the original area of caseous pneumonia. These vessels, since they are completely surrounded by diseased lung tissue, are soon obliterated by an intimal proliferation or more rarely by an organization of a thrombus within the lumen of the artery (Pauli (13)). Since these arteries are rich in elastic fibres and since the elastic fibres are resistant to the caseous tuberculous process, therefore, these blood vessels remain intact. When liquefaction takes place within the caseous area the obliterated blood vessels remain

intact and represent the trabeculae which traverse the cavity. Only when such trabeculae contain a patent arterial lumen may an aneurysm develop within them.

The pulmonary artery, on the other hand, in which the aneurysm develops, lies outside the tuberculous cavity. This vessel as it approaches the vomica will encroach upon the outer wall of the cavity in one area. The artery, except in the one area where it encroaches upon the cavity, is surrounded by normal lung tissue and is patent. The outer wall of the cavity is composed of productive tissue. The productive tissue destroys the elastic fibres of the vessel wall where the artery encroaches on the cavity and an aneurysm develops in this area.

An irregular rent was present in the dome of the aneurysm in almost all of the 38 patients who died as a result of rupture of the aneurysm. Thrombi have been found attached to the inner wall of an aneurysm, particularly when the aneurysm was large, but are absent from the vast majority of aneurysms in our series. Huebschmann (14), on the other hand, found that the aneurysms frequently contained thrombi.

In the cases dying of ruptured aneurysm, blood filled all the cavities in both lungs, the trachea and the bronchi. Aspirated blood was noted in both lungs particularly in the lower lobes. In two cases in which the draining bronchus of the cavity containing the ruptured aneurysm was occluded, haemorrhage was present only within the cavity.

The size of the aneurysm depends upon the calibre of the artery in which it develops, the average diameter of the lumen being 1 to 5 millimetres (Menetrier (4), Eppinger (2)). In occasional cases a large

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FIG. 1. An aneurysmatic dilatation (a) of a branch of the pulmonary artery lying in a chronic cavity (b). The aneurysm had not ruptured and had been an incidental finding at necropsy.

FIG. 2. Case 1. A ruptured aneurysm of a branch of the pulmonary artery (a) lying in a chronic excavation (b). A probe passes through the perforation (c).

FIG. 3. Case 2. A ruptured aneurysm of a branch of the pulmonary artery (a) which almost fills the cavity. A large rent is present in the dome of the aneurysm (b).

FIG. 4. Case 3. A probe passes through a rupture of an aneurysm of a branch of the right lower lobe pulmonary artery (a). The wall of the cavity which contains the aneurysm is stained red by the retained blood while the other excavations contain no blood. The blood from the ruptured aneurysm is retained in this cavity because of the occluded bronchus (b) leading into the excavation containing the ruptured aneurysm.

FIG. 5. A three centimetre aneurysm of a branch of the pulmonary artery which almost completely fills a chronic tuberculous excavation (a). The blood clot contained within the aneurysm is intimately attached to the blood vessel wall, although this individual did not die of a fatal haemorrhage. The patient gave a history of repeated haemorrhages, the last one of which occurred two months before death.

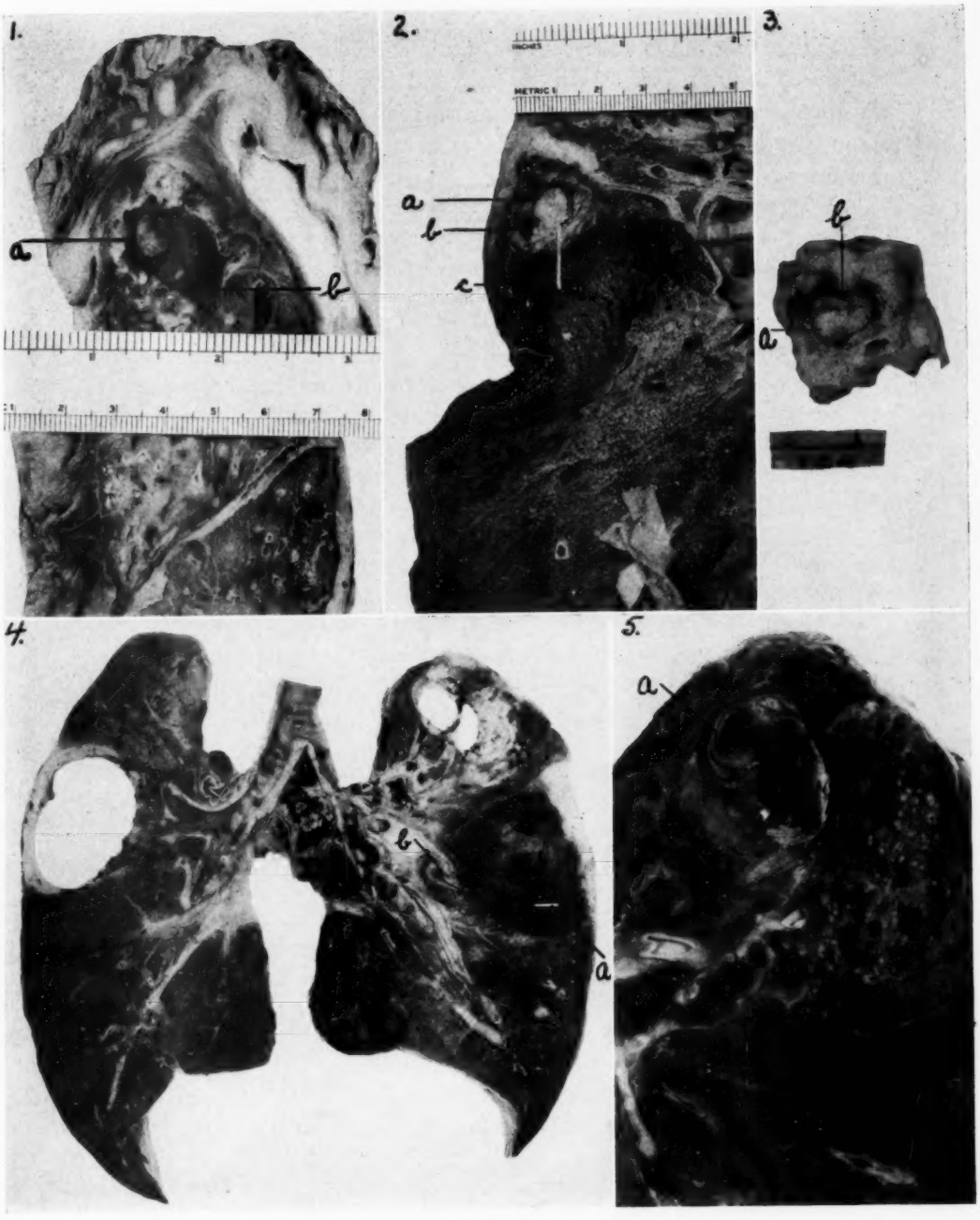

PLATE 1

aneurysm may almost completely occupy the entire excavation. Although the size of the aneurysm was not recorded in all of our cases, one measured 2 cm., another 3 cm., and several ranged from 5 mm. to 1 cm. In three aneurysms studied in detail the diameter of the lumina of the pulmonry arteries was 1.0, 1.0 and 3.0 mm. respectively. The clinical histories of these three cases follows.

Case 1: F. S., a 47 year old white female whose father died of chronic pulmonary tuberculosis, was admitted to Sea View Hospital on January 12, 1936. Two years before admission she had developed pleuritic pain, cough, night sweats and slight expectoration. Her sputum was positive for acid-fast bacilli. After six months of bed-rest in a sanatorium her sputum became negative and she was discharged. After eighteen months at home she presented herself in a municipal tuberculosis clinic for examination and treatment. Her sputum was positive and she was recommended for admission to Sea View Hospital. On admission the patient was markedly dyspnoeic, but not acutely ill.

Laboratory findings: The sputum varied from negative to Gaffky IV. The red count was 5,150,000; white blood cells 9,500; polynuclears 63 per cent; lymphocytes 28 per cent; monocytes 12 per cent; eosinophiles 2 per cent.

Roentgen examination of the chest revealed a definite cavity behind the clavicle on the right and a small annular shadow immediately below the cavity. There was a scattered nodular infiltration throughout the right lung. The left lung showed a hazy shadow in the peripheral portion in the region of the second and third ribs.

Course: Following admission the patient showed continuous clinical improvement until suddenly at 11:45 a.m. on June 23, 1937, she had a sudden large pulmonary haemorrhage and expired immediately.

Necropsy: The body was that of a well developed and fairly well nourished white female. The trachea, bronchi and stomach were filled with blood. Both upper lobes contained large amounts of fibrous tissue and were contracted. The middle and both lower lobes were emphysematous. Two thick-walled cavities were present, one in the posterior aspect of the right upper lobe and the other, 25 by 16 mm., in the apical portion of the posterior aspect of the left lower lobe. Both were filled with clotted blood and the left contained a ruptured aneurysm of a branch of the left lower lobe pulmonary artery which measured 7 mm. in diameter. Encapsulated caseous calcified foci and aspirated blood were present throughout both lower lobes.

Case 2: A. B., a 26 year old white female, was admitted to Sea View Hospital on June 3, 1936. In September, 1934, she began to cough and noticed fatigue

and weakness. Two months later she was admitted to a municipal tuberculosis sanatorium with an established diagnosis of pulmonary tuberculosis. A left artificial pneumothorax was induced. Her sputa examinations were alternately negative and positive until, on June 3, 1936, she was transferred to Sea View Hospital for severance of the adhesions in the left pleural cavity and induction of a right artificial pneumothorax. On admission to Sea View Hospital the patient appeared chronically ill.

Laboratory findings: The sputum varied from Gaffky V to X. The haemoglobin was 69 per cent; red blood cells 3,680,000; white blood cells 10,350. The urine, blood chemistry and blood Wassermann tests were negative.

Roentgen examination of the chest on June 3, 1936, revealed a hydropneumothorax on the left with an irregular collapse of the left lung. There was caseous pneumonic tuberculosis of the right upper lobe.

Course: The patient's condition became progressively worse and she refused permission for the cutting of the adhesions on the left side. Her pneumothorax was continued until July 23, 1936, when she refused to have further refills. In her last three weeks of life her dyspnoea became more marked.

Roentgenographic study of the chest on November 5, 1936, gave evidence of increased involvement on the right side including large caseous pneumonic and exudative lesions in the midportion of the right lung field. On the left side there was reëxpansion of the pneumothorax and a caseous pneumonic lesion with an excavation below the clavicle.

Two days later, at 11:30 p.m., the patient had a massive pulmonary haemorrhage and died within a few minutes.

Necropsy: The body was that of an emaciated white female whose trachea, bronchi and stomach were filled with blood. The left lung was partially compressed, showed an increase of fibrous tissue and in the upper third of the posterior aspect of its upper lobe there was an excavation 2 cm. in diameter. Throughout the right lung there were numerous excavations filled with blood clots. One in the anterior aspect of the right lower lobe was almost completely occupied by a pulmonary aneurysm, 1 cm. in diameter, and showing a tear within its wall. Throughout the remainder of both lungs were acinous and encapsulated caseous foci. The caecum and appendix contained numerous ulcers with overhanging edges and a dirty gray base, ranging up to 1 cm. in diameter.

Case 3: P. B., a 50 year old white male, was well until suddenly, in April, 1936, while running for an elevator, he coughed up about one quart of blood. He was admitted to a municipal tuberculosis hospital where chronic pulmonary tuberculosis was diagnosed by roentgen examination and a positive sputum. On June 6, 1936 he was transferred to Sea View Hospital. On admission the patient did not appear acutely ill.

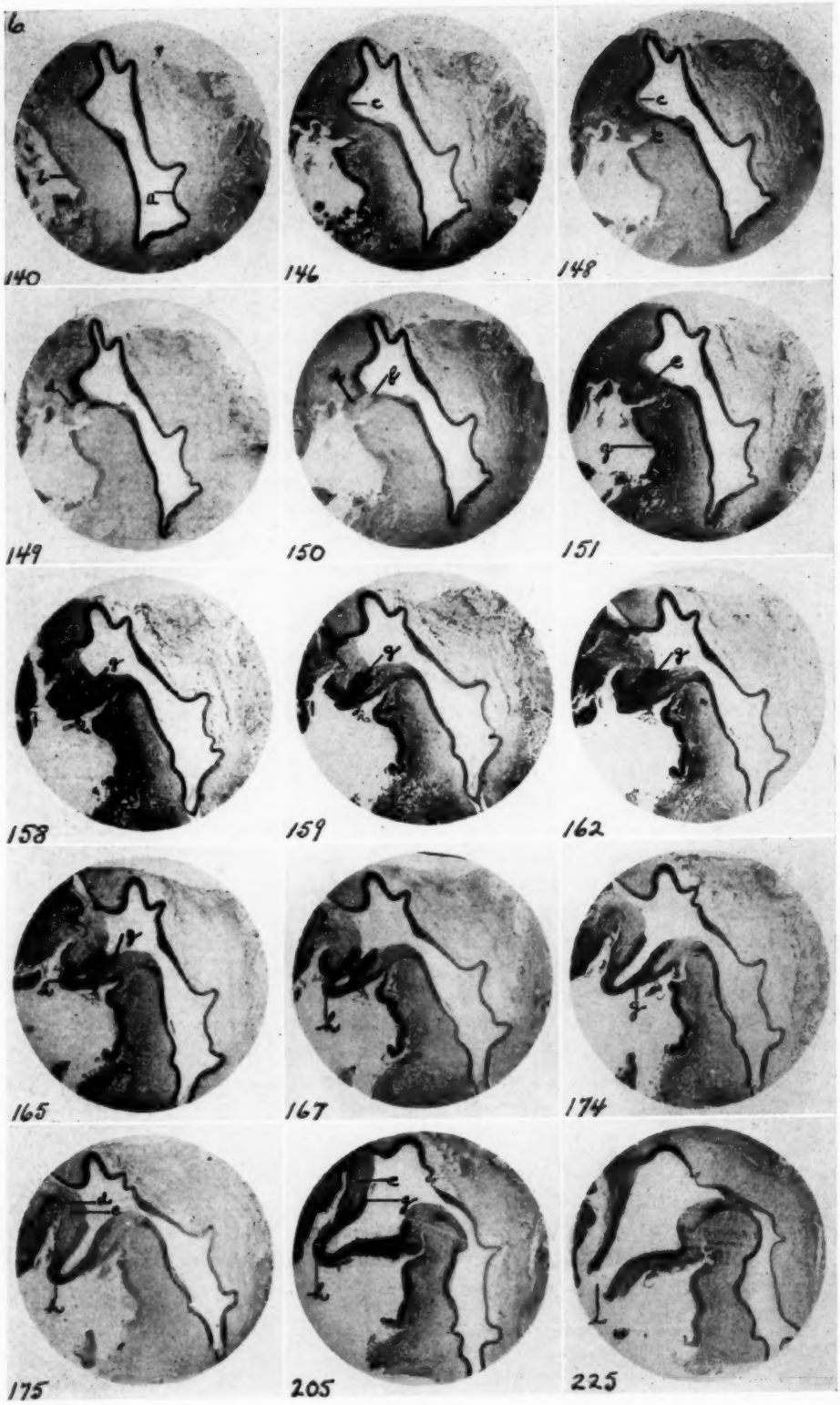

PLATE 2

Laboratory findings: The sputum varied from Gaffky IV to X. The blood sedimentation rate was 56 mm. in 45 minutes.

Roentgen examination of the chest on July 1, 1936 revealed irregular exudative lesions at the root of the right lung and axillary portion of the left infraclavicular area. There was an acinous spread to the basal and axillary portion of the right upper and lower lobes.

Course: The patient's condition became progressively worse. On October 6, 1936, a second roentgen examination of the chest showed a definite annular shadow in the lateral portion of the left lung at the level of the fourth rib and a caseous pneumonic lesion on the right side with several annular shadows in the upper portion of the lung. There was extensive acinous nodular infiltration throughout both lungs. Six months later (March 2, 1937) roent-

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FIG. 6. Photomicrographs of representative sections in the formation of the pulmonary arterial aneurysm in case 2.

Slide No. 140. The normal pulmonary artery (a) lies near the tuberculous cavity (b). (Elastica-Van Gieson stain.)

Slide No. 146. There is an intimal thickening (c) of the artery where the vessel lies closest to the cavity wall. (Elastica-Van Gieson stain.)

Slide No. 148. The intimal thickening (c) is greater. There is now a beginning destruction of the elastic fibres (d) of the adventitia by the granulation tissue of the outer wall of the cavity (e). (Elastica-Van Gieson stain.)

Slide No. 149. The elastic fibres (d) of the arterial wall have been completely destroyed in this area. (Elastica-Van Gieson stain.)

Slide No. 150. The tapered ends of the destroyed elastic fibres (d) are further separated. The granulation tissue of the cavity wall fuses with the thickened intima (f). (Elastica-Van Gieson stain.)

Slide No. 151. A greater part of the vessel wall is replaced by the granulation tissue of the cavity wall (e). A pyogenic membrane (fibrin layer) (g) forms the inner wall of the cavity. (Hematoxylin-eosin stain.)

Slide No. 158. The fibrin layer (g) extends toward the artery. (Hematoxylin-eosin stain.)

Slide No. 159. There is further progression of the fibrin (g) toward the inner wall of the artery. (Hematoxylin-eosin stain.)

Slide No. 162. The fibrin layer (g) has reached the inner surface of the vessel and replaces the cavity and vessel wall in this area. (Hematoxylin-eosin stain.)

Slide No. 165. The fibrin layer (g) extends to either side to replace the granulation tissue. There is now an aneurysmatic bulge (h) into the lumen of the cavity. (Elastica-Van Gieson stain.)

Slide No. 167. The aneurysmatic bulge (h) is more pronounced. (Hematoxylin-eosin stain.)

Slide No. 174. The fused arterial wall and cavity wall formed by the fibrinoid material (g) are not distinguishable. (Hematoxylin-eosin stain.)

Slide No. 175. The aneurysmatic bulge (h) is more marked. The elastic fibres (d) taper off into the granulation tissue (e). (Elastica-Van Gieson stain.)

Slide No. 205. The aneurysmatic bulge (h) is now quite marked. The fibrinoid material (g) has extended further into the granulation tissue (e). (Elastica-Van Gieson stain.)

Slide No. 225. Rupture of the aneurysm (I).

genographic examination showed a marked increase in the size of the cavities of both upper lung fields with an otherwise unchanged infiltration. A small fluid level was noted at the base of the large cavity on the right side. During the three months before death the patient experienced a number of haemoptyses. One of these was approximately five ounces. At 12:30 p.m., April 2, 1937, he suddenly became markedly dyspnoeic and cyanotic. The pulse was regular and of low tension. There were numerous large moist râles over the lungs anteriorly and posteriorly. The heart sounds were scarcely audible. An hour later he died.

The final clinical diagnosis was (*1*) chronic pulmonary tuberculosis, (*2*) myocardial failure secondary to pulmonary insufficiency.

Necropsy: The body was that of a well developed obese white male. Large tuberculous excavations were present in both the left and right upper lobes and in the right lower lobe. Numerous patent bronchi communicated with the cavities in the upper lobes, which were lined with dirty gray membranes to which caseous particles were attached. The excavation in the right lower lobe measured 7.5 by 5.5 cm. and was completely filled with a blood clot, removal of which disclosed a trabecula traversing the floor of the cavity with an aneurysmatic bulge 7 mm. in diameter, 4 cm. from the medial border of the cavity. There was a perforation in the lateral wall of the bulge and the branch of the right lower lobe bronchus leading into the excavation was occluded. Encapsulated caseous foci were present in the remainder of the right lung but there was no blood in any other part of this lung or in the left lung, trachea or bronchi.

HISTOPATHOLOGY

The pulmonary aneurysms from the three cases whose histories have just been presented were studied in detail. A total of 1,057, 1,510, and 950 sections respectively were examined.

The tissue studied included the normal pulmonary artery approaching the cavity wall through the aneurysmatic dilatation and the cavity wall. Serial sections were made beginning with normal arterial wall and continuing through the entire aneurysm. Two to four sections were placed on a slide. Every fifth slide (sometimes more frequently) was stained with elastica-Van Gieson, every ninth slide was stained for acid-fast bacilli by the Ziehl-Neelsen method. All other slides were stained with hematoxylin-eosin.

All three cases, with the exception of minor variations, showed the following histological changes:

The first changes to be observed in the wall of the pulmonary artery are in the intima as the artery approaches the cavity wall. In a small

area adjacent to the cavity wall, there is a subendothelial increase of connective tissue. As the artery nears the cavity, the adventitia of the vessel is encroached upon by the outer wall of the vomica in a circumscribed area. (In the first two cases this granulation tissue of the outer wall of the cavity is nonspecific; in the third case the granulation tissue invading the adventitia of the artery is tuberculous and contains epithelioid and giant cells.) As the artery more closely approaches the cavity there is progressive extension of the granulation tissue from the adventitia into the media of the blood vessel wall, the granulation tissue destroying and replacing the elastic fibres.

The granulation tissue of the outer wall of the cavity so completely replaces the adventitia and the media that the artery and cavity wall are fused in this circumscribed area. It was this gradual destruction of the pulmonary arterial wall in a circumscribed area by the granulation tissue of the cavity wall that led Eppinger (2) to name this type of dilatation "erosion aneurysm."

Concomitant with invasion of the arterial wall by granulation tissue from without, there is progressive thickening of the intima by connective tissue, which fuses with the granulation tissue replacing the adventitia and the media.

The inner wall of the cavity (pyogenic membrane) is composed of a fibrinoid substance containing polymorphonuclear leucocytes and lymphocytes. At the point where the granulation tissue that replaced the adventitia and media has fused with the thickened connective tissue layer of the intima, the fibrinoid material progresses from the inner wall of the cavity outward onto the adjacent blood vessel wall until it replaces the entire vessel wall in this area, after which it is no longer possible to distinguish between cavity and arterial wall.

After the migration of the fibrinoid material ceases, there occurs a protrusion of the vessel into the lumen of the cavity, this protrusion occurring in the circumscribed area of the arterial wall where the elastic fibres have been completely destroyed and replaced by the granulation tissue of the cavity wall. The granulation tissue on each side of the fibrinoid material within the wall becomes gradually more extensive with encroachment of the cavity wall upon the vessel wall until a fairly wide area of the vessel wall is replaced by cavity wall. However, the invading granulation tissue tapers off in the region of the artery not encroached upon by the cavity wall. An important finding is that the elastic fibres of the vessel in this area do not end abruptly, but thin out

from the healthy portion of the vessel until they disappear gradually in granulation tissue. The fibrinoid material becomes more extensive until it actually supplants the granulation tissue, that, earlier, replaced a large area of the vessel wall. The protrusion of the vessel likewise becomes thinner, rupture usually occurring at the site of greatest thinning. The portion of the artery not in contact with the wall of the cavity shows no evidence of pathological change.

DISCUSSION

Much controversy exists as to the nature, origin and significance of the fibrinoid material forming the wall of the aneurysm. According to Meyer (5), who has designated the fibrinoid substance "hyaline membrane," the process proceeds in the following manner:

While the adventitia and media are being destroyed in a circumscribed area by the invasion of granulation tissue, the intima remains as the only intact coat of the vessel in the region of the cavity wall. The leucocytes and red blood cells within the lumen of the vessel attach themselves to the internal surface of the intima, where they accumulate to form a "white blood clot" containing fibrinous reticulum, thus doubling the size of the wall which is in danger of rupturing. Actually, the fibrinous reticulum extends outward until it generally replaces the granulation tissue within the arterial wall, as well as the wall of the cavity in this area, and then undergoes a special degeneration, or hyaline transformation. This hyaline transformation was designated by Meyer (5) as the "hyaline membrane." The pulmonary aneurysm forms after the dilatation of this hyaline membrane. Meyer described the membrane as particularly strong and resistant.

In the three cases which we studied in detail, we were unable to note any intimal accumulation of blood elements as described by Meyer.

Eppinger (2) believes that Meyer (5) erroneously endows the dead hyaline material with power to become an active process, capable of new formation, substitution and growing together with living tissue. Eppinger is of the opinion that hyaline degeneration is a peculiar tissue necrosis and that, like all necrotic processes, it is the result of nutritional disturbances. Eppinger postulates that after the adventitia and media have been destroyed and replaced by granulation tissue, this tissue undergoes hyalinization and then caseous necrosis. He holds that the hyalinization of the arterial wall occurs under the influence of tubercle bacilli (tuberculinization) or through the action of fluids present in the pulmonary cavities.

We cannot agree with Eppinger (2) that the granulation tissue which replaces the vessel wall first undergoes hyalinization and then caseation as it progresses from the inner part of the cavity toward the lumen of the artery, or that the "hyalinization of the arterial wall," as he calls it, is due to the influence of tubercle bacilli or occurs under the action of fluids found in the cavity.

Our findings concur with those of Meyer (5), namely, that the hyaline formation (fibrin extending from the inner wall of the cavity) is an active process capable of progression and fusion with living tissue.

On the other hand, we agree with Eppinger (2) that the hyaline membrane originates in the cavity wall and progresses thence to the blood vessel. In the three cases studied it was found that after the adventitia and media had been replaced by the granulation tissue of the cavity wall, there occurred an extension of the fibrinous material from the inner wall of the cavity toward the adventitia. The greater part of the inner wall of the cavity is formed by a pyogenic membrane composed of interwoven bands of fibrin (observed with Mallory's fibrin stain) and containing within its meshes numerous polymorphonuclear leucocytes and lymphocytes and in its later stages fibroblasts and epithelioid cells.

It appears that, immediately following the fusion of the vessel and cavity through the complete replacement of the arterial wall by the granulation tissue of the cavity wall, there is a marked increase of fibrin in the pyogenic membrane in this region. The fibrin not only extends to the intima, but continues to replace the granulation tissue invading the arterial wall on either side. Widening of the vessel and its protrusion into the lumen of the cavity occur after the replacement of the granulation tissue by the fibrin.

We wonder whether the difference of opinion between Meyer (5) and Eppinger (2) may not be accounted for by differences in approach to the study of this problem. Eppinger studied aneurysms of the pulmonary artery as well as the pulmonary cavity by means of serial sections. Meyer did not make serial sections but studied histological sections by dividing the tissue into small portions perpendicular to its axis.

In our cases the extension of the fibrin from the inner wall of the cavity to the vascular wall occurred within eight to ten sections. Since the sections were cut to five micra one may see that the complete extension of the fibrin from the cavity wall to the blood vessel occurred in a distance of 40 to 50 micra. After the fibrin has extended from the cavity wall into the wall of the blood vessel it is no longer possible to determine whether the fibrinoid material originated from the cavity

wall or from the blood vessel wall. Since this extension occurs within such a short distance, it is easy to overlook it unless serial sections are studied.

That the hyaline membrane (fibrinoid layer) is especially resistant to the pressure in the pulmonary artery, as Meyer (5) states, is difficult to believe. Our study indicates that in the presence of a hyaline membrane there is weakening of the wall, evidenced by the progressive enlargement of the aneurysmatic dilatation with rupture of the vessel eventually occurring at the thinnest point of the aneurysm.

Is this rupture the result of a sudden increase in intrapulmonary pressure?

Letulle (12) long ago expressed the view that the wall of the aneurysm ruptures where it lies exposed in the cavity as a result of its gradual erosion by tubercle bacilli. This view is generally discarded to-day.

Bogen (11), who made a very exact study of 4,000 instances of pulmonary haemorrhage in 450 patients, believes that the factors tending to increase the blood pressure in the pulmonary circulation are important in the production of the rupture. He found that haemorrhage occurred most frequently when activity was greatest, that is, the rising hour, during the walking period, and at meal time. It seems to us, however, that the findings of Bogen are coincidental in that the basic pathological process is a weakening of the arterial wall with destruction of the elastic fibres. Lack of resistance in one part of the wall as a result of this destruction of the elastic tissue makes it possible for the wall to dilate under the influence of pulmonary arterial pressure. With dilatation there is a simultaneous thinning of the wall until rupture occurs in the portion of the wall no longer able to resist the pressure.

Regarding the conditions necessary for the development of an aneurysm of the pulmonary artery, Jaffé (15), Kasper (16) and others are of the opinion that proliferative changes in the intima occlude the artery before the destructive process of tuberculosis involves the vessel. Graeff (17) and Jaffé contend that the extension of caseation of the surrounding tissue to the adventitia, media and intimal elastic membrane with consequent destruction of the elastic fibres is so rapid as to allow no time for intimal proliferation sufficient to occlude the vessel. According to Jaffé and Graeff the aneurysm develops as a result of an active tuberculous process.

Our own studies and a review of the data accumulated by Eppinger (2), Meyer (5) and Menetrier (4) have convinced us that the process is

different from the one just described. We have found, as described above, that the aneurysm develops as a result of the progressive destruction and replacement of the elastic fibres of the pulmonary artery from without inward by granulation tissue from the outer cavity wall. As the cavity undergoes progressive healing the granulation tissue within its wall continuously increases. Where an aneurysm of the pulmonary artery develops the vessel approaches a cavity wall tangentially. As the wall of the cavity enlarges due to an increase of granulation tissue, that portion of the vessel wall closest to the cavity is encroached upon by the granulation tissue. This granulation tissue, which extends toward the intima, destroys the elastic fibres of the artery in a circumscribed area, and it is this weakened area that becomes the site of aneurysmatic dilatation.

The truth of this hypothesis that aneurysm develops as a result of healing changes would seem to be clinically substantiated by the fact that 28, or more than half (62 per cent) of our 45 cases of pulmonary artery aneurysm, suffered from chronic pulmonary tuberculosis for a period varying between two and nineteen years, confirming the findings of others that the tendency is for an aneurysm to develop in a chronic cavity. Were it otherwise, more aneurysms would be seen inasmuch as the vast majority of cases of pulmonary tuberculosis coming to necropsy have a history of tuberculosis of less than two years duration. It is not unusual, also, to observe a ruptured pulmonary aneurysm in an individual with an "arrested" form of pulmonary tuberculosis.

CONCLUSIONS

1. In 1,114 cases of ulcerative pulmonary tuberculosis in Sea View Hospital, 45 pulmonary arterial aneurysms were found at autopsy.

2. Aneurysms were found in 34 white individuals and in 11 Negroes. The age incidence ranged from twenty to sixty-five years, the greatest incidence being in the twenty to forty year age group.

3. The aneurysmatic dilatations were present in chronic cavities and in the left lung more frequently than the right. The size of the aneurysm in recorded cases varied from 5 mm. to 3 cm. The size of the cavity bore no relation to the size of the aneurysm.

4. Serial sections of three aneurysms studied in detail indicate that the pathogenesis of aneurysm of the pulmonary artery is as follows: (*a*) The adventitia and media of the artery are replaced by granulation tissue from the cavity wall as the vessel encroaches upon the vomica.

This replacement is preceded by an intimal thickening in the involved region. (*b*) Immediately following the replacement of the adventitia and media by granulation tissue, the fibrin membrane of the inner wall of the cavity in this region extends to the intima of the vessel. (*c*) When the fibrin has completely replaced the fused cavity wall and artery in the circumscribed area, there occurs a bulge of this portion of the vessel into the lumen of the cavity. (*d*) The bulge of the vessel becomes progressively larger until it causes a tear in the thinnest portion of the wall.

5. Aneurysms of the pulmonary artery develop in chronic cavities in which extensive healing changes have taken place. The progressive healing in the cavity brings about an increase of granulation tissue. The latter encroaches on a pulmonary artery in a circumscribed area and results in a destruction of the elastic fibres. This weakened area becomes the site of an aneurysmatic dilatation.

6. Twenty-eight, or 62 per cent, of the 45 cases dying of ruptured pulmonary artery aneurysm at Sea View Hospital gave a history of chronic pulmonary tuberculosis from two to nineteen years, which supports our conclusion that aneurysms of the pulmonary artery tend to develop in the more chronic forms of pulmonary tuberculosis.

I wish to express my appreciation to Dr. Samuel Lipstein for his help in the preparation of this paper.

REFERENCES

(1) LAENNEC, R. T. H.: Traité de l'auscultation médiate et des maladies des poumons et du coeur, ed. 4, P. Andral, Paris, 1837, vol. 2.

(2) EPPINGER, H.: Pathogenesis (Histogenesis und Aetiologie der Aneurysmen), Archiv. f. klin. Chirur., Supplement 1, 1887, *35*.

(3) FEARN, S. W.: Aneurysm of the pulmonary artery, Lancet, 1840–1841, *1*, 679.

(4) MENETRIER, M.: Des aneurysmes et des lésions vasculaires tuberculeuses specifiques dans les cavernes de la phtisie pulmonaire chronique, Archives de méd. exp., 1890, *2*, 97.

(5) MEYER, P.: De la formation et du role de l'hyaline dans les aneurysmes et dans vaisseux, Archives de physiol. normale et pathol., second series, 1880, *7*, 598.

(6) PAGEL, W., AND HENKE, F.: Lungentuberkulose in Henke und Lubarsch, Handbuch d. spez. path. anat., 1930, *3*, part 2, p. 139.

(7) RASMUSSEN, V.: On hemoptysis, especially when fatal, in its anatomical and clinical aspects, (translated from the Hospitals-Tidende, eleventh year, Nos. 9–13, Copenhagen, February and March, 1868, by William Daniel Moore), Edinburgh Med. Jour., 1868, *14*, 385 and 486.

(8) POWELL, R. D.: Excavation of the lung in phthisis, Lancet, 1877, *2*, 793.

(9) PINNER, M., AND KASPER, J. A.: Pathological peculiarities of tuberculosis in the American Negro, Amer. Rev. Tuberc., 1932, *26*, 463.

(10) FRAENTZEL: Beobachtungen ueber das Vorkommen grosser Lungenblutungen, ihren Ursachen und ihren Verlauf, Charité- Annalen II, 1877, 365.
(11) BOGEN, E.: The pathogenesis of tuberculous hemoptysis, Amer. Jour. Clinical Path., 1932, *2*, 299.
(12) LETULLE, M.: Anatomie pathologique, 1936, *2*, 776.
(13) PAULI, P. A.: Ueber Veraenderung von Arterien in Cavernen bei Phthsis Pulmonum, Virchows Arch. f. path. Anat., 1897, *77*, 69.
(14) HUEBSCHMANN, P.: Pathologische Anatomie der Tuberkulose, J. Springer, Berlin, 1928.
(15) JAFFÉ, R. H.: The pathology of pulmonary tuberculosis, Goldberg's Clinical Tuberculosis, vol. 1, 1935, p. 97.
(16) KASPER, M.: Ueber die Veraenderungen an den Blutgefässen im Bereich tuberkuloeser Lungenkavernen, Beitr. Klin. Tuberk., 1932, *80*, 537.
(17) GRAEFF, S.: Die Kaverne der Lungentuberkulose vom pathologisch-anatomischen Standpunkt aus, Ergebn. d. ges. Tuberkuloseforschung, 1935, *7*, 257.

VIRULENCE OF TUBERCLE BACILLI[1]

Its Variations Attendant on Animal Passage

KENNETH C. SMITHBURN

An understanding of the influence of host-to-host transmission on the virulence of tubercle bacilli is of importance to epidemiologists, clinicians, and laboratory workers. It is now established, largely through the work of European investigators, notably Griffith (1) and Jensen and Frimodt-Möller (2), that man may harbor attenuated as well as virulent tubercle bacilli; and it would be of value to epidemiologists to know whether the attenuated forms may attain greater virulence by host-to-host passage. Likewise, to clinicians engaged in programs of prevention by vaccination, especially with living microörganisms, it is essential to know whether, even occasionally, attenuated microörganisms may attain enhanced pathogenic properties. To laboratory workers such knowledge is of use in understanding the fundamental immunological behavior of the microörganisms; also it is desirable to know whether virulence can be maintained in order that standard cultures may be available for experimentation.

To review the literature on this subject would be to cite a series of conflicting results obtained by investigators here and abroad. However, it may be stated that, under certain circumstances, serially transferred strains have failed to attain enhanced virulence (Cummings (3), Willis (4), and Corper, Cohn and Damerow (5)) or have increased appreciably in their pathogenic properties (de Jong (6), and Jensen and Frimodt-Möller (7)). Pinner (13, 14) observed enhanced virulence after serial passage of atypical *Mycobacteria*. Other workers have reported irregular results in such experiments (de Jong (6, 8)), that is, in some instances cultures passed from host to host attained increased virulence, and in other instances they did not; and no rule seemed to govern the results obtained. Further, there have been reports that tubercle bacilli changed in type during animal transmission, especially in hosts resistant to the original type (Jensen and Frimodt-Möller (7)), the change involving an increase in pathogenic properties of the microörganisms.

[1] From the Laboratories of The Rockefeller Institute for Medical Research, New York.

Our earliest studies on the influence of serial passage were carried out by intraperitoneal primary inoculation of rabbits and subinoculation by the same route of tissue suspensions. About the same time we were conducting experiments on intracerebral inoculation. In these experiments we noted the extraordinary multiplication of tubercle bacilli in brain and meninges and the marked susceptibility of guinea pigs to very small doses of virulent bacilli (9). It was decided to test serial passage by this route as a means of altering the virulence of tubercle bacilli.

MATERIALS AND METHODS

Bacteria: Three strains of tubercle bacilli were used in the experiments: the well known bovine strain B1, our line of which has become markedly attenuated; another bovine strain, 39, grown at pH 6.4 and rather markedly attenuated (10); and the well known Saranac human strain H37. The B1 and H37 strains were grown on Corper's (11) glycerolated egg-yolk medium adjusted to pH 6.8. The line of the bovine strain 39 used was grown on the same medium adjusted to pH 6.4 (10). Suspensions of the bacteria were prepared by grinding a weighed quantity of bacilli freshly removed from the culture tube, with sterile physiological saline in a sterile mortar, so that 1 cc. of suspension contained 1 mg. of bacilli. Serial decimal dilutions were then made with saline until the desired mass of microörganisms was contained in 0.1 cc. of suspension.

Animals: The rabbits used in the first experiment were gray chinchilla males bred at the Rockefeller Institute. The guinea pigs were albinos bred at this Institute, mostly weighing about 400 gm. In the final tests of comparative virulence animals were carefully selected according to weight and sex, so that the groups were as nearly alike as possible. All guinea pigs were of stock free from epizoötic streptococcal infection.

Transmission: Among the rabbits, serial transfers were made by removing aseptically the spleen and omentum, grinding these in a sterile mortar with sterile saline, with or without the aid of sterile sand. This crude suspension was cleared of large particles by centrifuging at low speed for two to five minutes, and the supernatant fluids were used for inoculation by the intraperitoneal route. In the case of guinea pigs, the brains were removed aseptically, the right hemispheres being used for subinoculation, and the suspensions prepared as above except that it was not necessary to grind the brains with the aid of sand. Subinoculation of brain was made with 0.1 cc. of a 20 per cent suspension.

Intracerebral inoculation: Anaesthesia was induced by ether or by intraperitoneal injection of seconal[2] (20 mg. per kilo). Animals recovered from the ether more quickly but with seconal anaesthesia we have encountered fewer pulmonary sequelae than with ether, and the anaesthesia so induced is quite adequate for this operation. The technique of inoculation was the same as previously described (9).

Measurement of results: From the beginning of the experiments it was considered inadvisable to rely upon the longevity following inoculation or upon extent of lesions in the animals of any serial passage, since individual variation in resistance might seriously influence such results. Instead, animals were first inoculated with culture material, transmissions in series were then made with brain suspensions (spleen and omentum in the rabbits), and the bacilli were recovered in culture from animals of the final series. When the recovered culture had grown it was transferred once to fresh medium (Corper's, pH 6.8) and at the same time the stock or starting culture was transferred. These "stock" and "passage" cultures were then inoculated in identical doses into comparable groups of guinea pigs by the intracerebral route. Mean survival of a group of animals was used as the criterion of virulence.

FIRST EXPERIMENT

Three male chinchilla rabbits, about six months old, were each inoculated intraperitoneally with 2.0 mg. bovine tubercle bacilli, strain B1 (attenuated). Eleven days later one animal was sacrificed and its spleen, omentum and retrosternal lymph nodes were suspended in saline solution for serial inoculation of a second rabbit. The latter was similarly sacrificed after eleven days and its tissues used for inoculation of a third serial animal. A fourth passage was done similarly eleven days later.

Of the two remaining animals of the first series, one was sacrificed for pathological survey thirty days after inoculation and showed a moderate amount of tuberculosis in the lungs, spleen, liver, testicles, retrosternal nodes, omentum and mesentery. The last animal of the first series was sacrificed 203 days after inoculation and showed some tuberculosis in the spleen, liver, omentum and testes, but considerably less than the animal described above. At the same time (170 days after inoculation) the animal of the fourth passage was sacrificed and it exhibited no tuberculosis.

[2] Sodium propyl-methyl-carbinyl allyl barbiturate, Lilly, supplied by Eli Lilly and Company, through Dr. G. F. Kempf, Indianapolis City Hospital.

This experiment demonstrated that the original bacilli were attenuated, that the lesions produced did not progress, and that by serial passage intraperitoneally at eleven-day intervals the virulence of the bacilli was not enhanced.

SECOND EXPERIMENT

Two female albino guinea pigs weighing 360 and 400 gm. respectively were inoculated intracerebrally under ether anaesthesia with 0.1 mg. of the attenuated line of bovine strain 39, grown at pH 6.4. Subinoculations in series were done from suspensions of brain. The experiment was terminated with the fifth serial passage when it was apparent that

TABLE 1

Guinea pigs in second transmission experiment showing intervals in days between passages and survival of animals not used for serial transmission

ANIMALS USED FOR PASSAGE	INOCULATED WITH	INTERVAL BETWEEN INOCULATION AND PASSAGE	OTHER ANIMALS NOT USED FOR TRANSMISSION	
			Number	Survival
		days		*days*
5770*	0.1 mg. bovine 39	14 S†	5771*	D† 34
5861	0.1 cc. 20% brain of 5770	15 S	5862	D 7
5959	0.1 cc. 20% brain of 5861	14 S	5958	S 163
6023	0.1 cc. 20% brain of 5959	15 S	6022	D 82
	0.1 cc. 20% brain of 6023		6036	S 124
			6037	S 124

* These are serial numbers used in this laboratory over many years.

† S indicates animal was sacrificed; D indicates animal succumbed.

no enhancement of virulence had taken place. Table 1 shows the protocol of this experiment.

In this experiment and the previous one the serial subinoculations were done at short intervals and it seemed possible that we had not allowed adequate time for the microörganisms to establish themselves and to multiply sufficiently before the passages were made. Accordingly, in a third experiment the attenuated B1 strain was again used and the first subinoculation was not done until an animal of the first series succumbed. Thereafter subinoculations were done at somewhat earlier intervals, but only when the temperature curve or clinical condition indicated that the pathological process was well established. Temperatures reaching 104° F. or higher on four successive days, with or without paralysis, were considered evidence of active disease. Paralysis alone

was considered evidence of active disease, but there was almost invariably elevated temperature associated with it.

THIRD EXPERIMENT

The bovine strain B1 was used in this experiment. Three male guinea pigs weighing about 500 gm. each were inoculated intracerebrally with 0.1 mg. of this culture, after which serial intracerebral transmissions

TABLE 2

Guinea pigs used in third transmission experiment, showing intervals in days between passages and survival of animals not used for serial transmission

ANIMALS USED FOR PASSAGE	INOCULATED WITH	INTERVAL BETWEEN INOCULATION AND PASSAGE	OTHER ANIMALS NOT USED FOR TRANSMISSION		
			Number	Survival	
		days		*days*	
4709*	0.1 mg. bovine B1	66 D†	4710*	D 238	
4894	0.1 cc. 20% brain of 4709	25 S†	4893	S 21	
4970	Same from 4894	13 S	4971	D 60	
4991	Same from 4970	25 S	4990	D 52	
4995	Same from 4991	16 S	4996	D 39	
5000	Same from 4995	23 S	4999	S 16	
			5004	S 11	
5005	Same from 5000	35 S	5008	D 34	
			5009	D 150	
			5006	D 31	Inoculated
5015	Same from 5005	15 S	5007	D 36	from 5004
			5014	D 38	
5062	Same from 5015	12 S	5063	D 30	
			5077	D 28	
5079	Same from 5062	21 S cultures	5078	D 40	
			5080	D 28	
			5081	D 48	

* These are serial numbers used in this laboratory over many years.

† S indicates animal was sacrificed; D indicates animal succumbed.

were made with 0.1 cc. of a 20 per cent suspension of the right cerebral hemisphere. In this manner ten serial passages of the microörganisms were made. Table 2 shows the protocol of this experiment and indicates the time intervals of each passage.

From the data shown in table 2, it may be seen that the survival time of animals not used for transmission, but allowed to succumb to the disease, became shorter as the bacilli were passed in series. This could have indicated either that more microörganisms were being transferred

with each serial passage, or that a quantitative change was taking place, namely, an enhancement of virulence of the bacilli. The actual amount of brain substance used for each serial inoculation was 20 mg. or less (0.1 cc. of 20 per cent suspension lightly centrifugalized). If the diminished survival time of animals in later series was due to increased numbers of bacilli, this amount of brain would, of necessity, have contained amounts of tubercle bacilli greater progressively than 0.5 per cent of its weight, which seems highly unlikely. That the cause of the progressive diminution in survival time was due to enhancement of virulence with serial passage is indicated by the subsequent tests of virulence.

The culture recovered from an animal of the tenth serial passage (5079, table 2), and a serial subculture of the original "stock" B1, were each transferred to fresh medium on the same day. When these cultures had grown out nicely, suspensions of each were made to the same density

TABLE 3

Mean and probable error of mean survival in days of animals inoculated with equal doses of "stock" and "passage" cultures of bovine tubercle bacilli, strain B1

DOSE	INOCULATED WITH STOCK B1. MEAN SURVIVAL DAYS	INOCULATED WITH PASSAGE B1. MEAN SURVIVAL DAYS	DIFFERENCE EXPRESSED AS MULTIPLE OF ITS OWN PROBABLE ERROR
mg.			
0.01	97.25 ±13.0	34.0 ± 3.4	4.72
0.000,1	93.25 ± 9.0	54.5 ± 1.5	4.24
0.000,001	132 ±17.8	112.0 ±15.6	0.84*

* Indicates difference is not statistically significant.

by weight (checked by examination of stained smears) and six groups each of four guinea pigs were inoculated intracerebrally, one group receiving 0.01 mg. of the "stock" culture, another group 0.000,1 mg., and a third group received 0.000,001 mg. each of this culture. The remaining three groups received at the same time identical doses of the "passage" culture. The twenty-four animals were allowed to succumb to the disease. Table 3 shows the mean survival time of each group, in days, and the probable error of each mean.

The results shown in table 3 demonstrated that the "passage" culture had acquired increased virulence, since the animals inoculated with either 0.01 mg. or 0.000,1 mg. succumbed more quickly, and significantly so, than the animals receiving identical doses of the "stock" culture. Moreover, the animals receiving 0.000,1 mg. of the "passage" culture died significantly earlier than those receiving 100 times this dose of the "stock" culture.

From experience gained in other experiments, it was clear, however, that the virulence of the "passage" culture, though definitely enhanced, was still substandard. Bovine strains of maximal virulence have, in our hands, caused death more quickly than did the "passage" line of the strain B1. However, from the experiment which follows it seems not unreasonable to assume that, with further host-to-host transmission, the microörganisms might have attained the maximal virulence of bovine tubercle bacilli.

Following this experiment it was decided to study the effect of host-to-host passage on a strain of microörganisms which was less attenuated than the two strains used in the earlier experiments. To this purpose our stock line of the human strain H37 was well suited since it was known to be of substandard virulence, but definitely pathogenic since susceptible animals inoculated with it inevitably eventually succumbed.

FOURTH EXPERIMENT

Four albino male guinea pigs each weighing about 400 gm. were inoculated intracerebrally, each with 0.01 mg. of the stock H37. All were allowed to succumb and the brain of the last survivor was used to prepare the inoculum for the two guinea pigs of the second series. In this manner the microörganisms were transmitted through five series of guinea pigs and were reisolated from an animal (5965) of the fifth series. This recovered culture and the stock line of H37 were transplanted at the same time to fresh medium, and when the bacilli were growing vigorously two groups of guinea pigs were inoculated intracerebrally with identical doses of the "stock" and "passage" lines.

Table 4 shows the protocols of animals used in transmission of the H37 strain. It will be noted that both animals of the third series suffered from intercurrent infection and it was necessary to treat the brain of guinea pig 5866 with 6 per cent sulphuric acid before passage. The acidulated brain suspension was carefully neutralized before inoculation into guinea pigs 5863, 5864 and 5888. The animals of the fourth and fifth series showed no evidence of intercurrent disease and the cultures recovered from guinea pigs 5964 and 5965 were not contaminated.

For comparing the virulence of the "stock" and "passage" lines of H37, two groups each of five albino male guinea pigs from the same breeding stock were selected. The individual weights of animals in the two groups were identical, and varied between 380 gm. and 480 gm., the mean for each group being 424 gm. The "stock" and "passage" cultures were each sixteen days old when used. One group of animals

received intracerebrally 0.000,01 mg. of the "stock" culture; each animal in the second group received by the same route an identical dose of the "passage" culture. Smears of the two inocula showed the bacilli to be

TABLE 4

Guinea pigs used in serial transmission of H37 strain, showing intervals in days between passages, and survival of animals not used for serial transmission

ANIMALS USED FOR PASSAGE	INOCULATED WITH	INTERVAL BETWEEN INOCULATION AND PASSAGE	OTHER ANIMALS NOT USED FOR TRANSMISSION	
			Number	Survival
		days		*days*
5739*	0.01 mg. stock H37	27 D†	5737*	D 21
			5738	D 21
			5740	D 23
5769	0.1 cc. 20% brain of 5739	12 D	5768	D 21
5866	0.1 cc. 20% brain of 5769	9 S‡	5865	D 9
5864	0.1 cc. 14.8% brain of 5866	14 S	5863	D 26
			5888	D 28
5965	0.1 cc. 20% brain of 5864	23 D cultures	5964	S 14 (moribund) cultures

* These are serial numbers used in this laboratory over many years.

† S indicates animal was sacrificed; D indicates animal succumbed.

‡Both animals suffering from intercurrent infection. Brain treated with 6 per cent H_2SO_4 and neutralized before passage.

TABLE 5

Individual survival and mean survival of groups of male albino guinea pigs inoculated with same dose of "passage" or "stock" H37

GUINEA PIG NUMBER	WEIGHT	H37 0.000,01 MG.	SURVIVAL DAYS	MEAN SURVIVAL DAYS
	gm.			
6304	380		22	
6305	420		26	
6306	460	"Passage" culture	33	27.6 ±1.3
6307	480		29	
6308	380		28	
6309	460		42	
6310	420		30	
6311	480	"Stock" culture	38	36.7 ±1.4
6312	380		38	
6313	380		34	

equally numerous and of similar morphology and staining characteristics. The two groups of animals were allowed to succumb. Table 5 shows the individual and mean survival time of these two groups of animals.

The difference between the mean for the two groups, 9.1 days, is 4.76 times the probable error of this difference. The odds against occurrence by chance of a difference of this order are greater than 700 to 1. It is therefore evident that the "passage" culture had been enhanced in virulence by serial passage. This and subsequent experiments have demonstrated that the "passage" line now has the maximal virulence characteristic of human tubercle bacilli.

HISTOLOGICAL STUDIES

Microscopical surveys of the tissues were made of all the animals of the first, third and fourth experiments. In the first experiment in which the attenuated microörganisms were not enhanced by passage, the animals of successive passages showed less tuberculosis (due either to healing, with death of the bacilli, or to dilution); and the rabbits of the third and fourth passages showed no lesions. In all of this series, wherever lesions were present they were of the chronic type described previously as being induced by attenuated microörganisms (12). In the fourth experiment employing the moderately attenuated H37 strain, all the lesions in animals of the "stock" and "passage" test groups, as well as the five groups of animals used for serial transmission, exhibited acute lesions of the type previously described as being induced by virulent microörganisms (12). Differences of note occurred, however, in the animals of the third experiment, in which the B1 strain, at first very attenuated, acquired greater virulence.

The animals of the first, second and third passages in the third experiment exhibited no microscopical lesions in lung, spleen, tracheal node or liver; the lesions in brain and meninges of the first series animals (4709 and 4710, table 2) were entirely of the chronic type and not extensive. In the second and third serial passages, however, lesions of the acute type began to occur, and the extent of lesions was greater. With successive serial transmissions there was an increase in the proportion of acute lesions, together with more extensive metastatic tuberculosis, particularly involving the spleen and liver. The animals of the tenth serial passage exhibited very extensive acute tuberculous meningoencephalitis and rather extensive metastatic lesions in liver, spleen, tracheal and cervical lymph nodes, but not in the lungs. Similar differences were noted in the animals used for final testing of virulence of "stock" and "passage" lines of bovine strain B1 (table 3). Here again those inoculated with the "stock" culture exhibited in the brain and

meninges sparse lesions entirely of the chronic (hard tubercle) type and little or no metastatic tuberculosis; but the animals receiving the "passage" culture exhibited almost wholly lesions of the acute type; and their lesions were more extensive not only in the brain and meninges, but in remote viscera as well. Moreover, the local and metastatic lesions of the "passage" animals showed many more tubercle bacilli, indicating greater capacity of the "passage" line of microörganisms to survive and multiply in the tissues of the host. These qualitative and quantitative differences in lesions were further evidence that, with host-to-host passage, there was a qualitative change in the bacteria.

DISCUSSION

The capacity of many species of bacteria to regain lost pathogenic properties during serial animal passage is so well known that in many laboratories serial passage is routinely employed to assure the maximal virulence of microörganisms for use in quantitative experiments. It is now obvious that the virulence of attenuated tubercle bacilli may be regained in part or *in toto* by serial passage intracerebrally in susceptible hosts. If the bacilli are markedly attenuated, the recovery of virulence is gradual, but if attenuation is moderate, virulence may be maximal after a few passages.

The failure of the microörganisms to regain virulence in our first two experiments was, in all probability, due to too rapid serial subinoculation, since the same strain of bacilli used in the first experiment did regain virulence in the third experiment. It seems probable that in order to enhance the virulence of markedly attenuated tubercle bacilli, serial passage should not be done earlier than the fourth week. But it is also obvious that if the bacilli be not too enfeebled at the beginning, serial subinoculation may be done earlier (fourth experiment); furthermore, with less attenuated microörganisms restoration of virulence is more rapid and more complete than when the microörganisms are very attenuated.

The prolonged survival time, wide spread in longevity between first and last deaths in a group, and consequent increase in the probable error of the mean, as shown in all groups of the third experiment receiving the "stock" culture, and the group receiving the smallest dose of "passage" culture (table 3), are typical of results we have obtained in other experiments in which we have used either attenuated microörganisms or very minute doses of virulent bacilli. In a considerable experience we have

found that death in such instances is not brought on by a generalized tuberculous meningitis, such as we have previously described (9). Instead the principal and often the sole lesion in such animals is almost invariably a circumscribed, indurated, gray-yellow nodule or plaque usually at the base of the brain, at or near the point of inoculation. Microscopical studies in such animals confirm the absence of generalized meningoencephalitis and reveal this nodule or plaque to be a sclerosed, more or less circumscribed tubercle, often of considerable size. If the lesion is large, there is usually a caseous centre in or around which are many tubercle bacilli; if small, it is usually noncaseous and few or no bacilli are present. It is as if the animal were able to localize very small numbers of virulent bacilli, or large numbers of attenuated microörganisms and to prevent their generalized dissemination but unable to destroy them in the localized focus. At this point a slowly progressive lesion develops which, by its size or intimate relation to vital cerebral centres, ultimately causes the death of the animal. Such were the findings in the animals of the third experiment inoculated with the "stock" culture (table 3). Some of the microörganisms in such lesions remain alive, multiply and, when transmitted in series through susceptible hosts, regain their virulence.

Much experimentation might be required to ascertain whether virulence may be enhanced through passage by other routes than the intracerebral. However, so far as we now know, the fundamental processes of the disease induced by intracerebral inoculation are not different from those of the disease induced by other means. It seems likely, therefore, that attenuated, living tubercle bacilli introduced by any route, so long as they remain alive, have the capacity, upon entering a new host, of acquiring greater virulence. Until such potential change can be ruled out, it would seem advisable that the injection of attenuated, living tubercle bacilli be confined to the practices of animal experimentation.

SUMMARY

The virulence of attenuated tubercle bacilli may be restored in part or *in toto* by serial brain-to-brain passage in guinea pigs. The restoration is more rapid and more complete if the attenuation be not too great. With reacquisition of virulence the tubercle bacilli possess greater power to survive and multiply within the host, and there is a change in the type of lesions induced from chronic to acute. These facts make possible the indefinite maintenance of virulence of standard lines of cultures.

Some possible implications of the results are discussed.

REFERENCES

(1) GRIFFITH, A. S.: Jour. Path. & Bact., 1914, *18*, 591.
(2) JENSEN, K. A., AND FRIMODT-MÖLLER, J.: Acta tuberc. Scand., 1936, *10*, 83.
(3) CUMMINGS, D. E.: Amer. Rev. Tuberc., 1932, *26*, 369.
(4) WILLIS, H. S.: Ibid., 1933, *28*, 884.
(5) CORPER, H. J., COHN, M. L., AND DAMEROW, A. P.: Ibid., 1936, *33*, 709.
(6) DE JONG, D. A.: Centralbl. f. Bakt., 1 Abt., Orig., 1905, *38*, 254.
(7) JENSEN, K. A., AND FRIMODT-MÖLLER, J.: Acta tuberc. Scandinav., 1936, *10*, 217.
(8) DE JONG, D. A.: Centralbl. f. Bakt., 1 Abt., Orig., 1905, *38*, 146.
(9) SMITHBURN, K. C.: Jour. Exper. Med., 1936, *64*, 771.
(10) SMITHBURN, K. C.: Amer. Rev. Tuberc., 1937, *36*, 637.
(11) CORPER, H. J., AND COHN, M. L.: Amer. Jour. Hyg., 1933, *18*, 1.
(12) SMITHBURN, K. C.: Amer. Rev. Tuberc., 1937, *36*, 659.
(13) PINNER, M.: Ibid., 1935, *32*, 424.
(14) PINNER, M.: Ibid., 1935, *32*, 440.

THE MULTIPLE PUNCTURE METHOD OF BCG VACCINATION[1,2]

SOL ROY ROSENTHAL

Weill-Hallé was the first to be entrusted with the vaccination of infants against tuberculosis by the use of BCG. He used the oral route for vaccinating but soon learned that only a small percentage of the infants thus vaccinated reacted to tuberculin (from 4 to 10 per cent after 3 months (Calmette)). Because it was assumed that a positive reaction to the tuberculin test indicated the presence of viable microorganisms and of tubercles in the host and thus a means of testing the efficiency of the vaccine, Weill-Hallé began to administer the vaccine by the subcutaneous route. He used 0.25 to 1 mg. but later reduced this dose to 0.01 and 0.02 mg. to diminish the extensive local reactions. Abscess formation following this method was not uncommon and at times months elapsed before complete healing because of the deep seated position of the lesions. To avoid the latter, Wallgren advocated and employed a single injection intracutaneously. Using an optimum dose of 0.1 mg. he obtained in 93 per cent of cases a positive tuberculin skin reaction. But this necessitated revaccinating 8 out of 35 cases. The local lesion usually suppurated after one month and healed after one to three months. In the series of Park and Kereszturi, up to 0.3 mg. was given in order to obtain 87 per cent positive reactors. Local necrosis followed in almost every case and in 25 per cent suppuration of the draining lymph nodes. After one year, 75 per cent reacted to the tuberculin test.

This brief sketch of the methods used in BCG vaccination indicates that the oral route is not reliable although its ease of application is not to be overlooked; the subcutaneous route results in deep seated abscesses which may have difficulty in draining, while the single intra-

[1] Presented at the joint medical session of the Pathological and Clinical Sections at the 34th annual meeting of the National Tuberculosis Association, Los Angeles, California, June 21, 1938.

[2] From the Tice Laboratories, a detail of the Municipal Tuberculosis Sanitarium (Dr. Frederick Tice, President), and the Department of Bacteriology and Public Health (Dr. Lloyd Arnold), University of Illinois College of Medicine, Chicago, Illinois.

cutaneous injection results in local lesions which usually suppurate, cause enlargement of the draining lymph nodes which may also suppurate, and finally the injection methods call for a more or less elaborate apparatus for administration.

A method was thus needed wherein the vaccine would have the following advantages:

1: Easily applied so as to afford a wider applicability
2: No gross local suppuration
3: No lymph node suppuration
4: Smaller doses without diminishing its efficacy

After attempting various methods (Rosenthal) the one of multiple punctures was chosen.

TABLE 1

The results of skin tests in guinea pigs vaccinated with BCG (multiple puncture method) using Old Tuberculin

NUMBER OF ANIMALS		1 WEEK	4 WEEKS	6 WEEKS	3 MONTHS	6 MONTHS	9 MONTHS	18 MONTHS	24 MONTHS
24	Per cent positive	58.3	70.6	90.9	95.2	93.0	100	100	100
	Average reaction	+	++	++	++	++	++	++	++
		8 x 10 +	10 x 12 ++	15 x 15 ++	15 x 15 ++	10 x 12 ++	12 x 15 ++	15 x 18 ++	15 x 15 ++

The figures in the second row represent mm., the upper + sign redness, the lower + sign induration, the number of signs represent the intensity of reaction.

Experimental studies: Guinea pigs were used for all animal experimentation. The hair on both sides of the spinal column in the lumbosacral area was shaved off and the skin was cleansed with alcohol and ether. Through a drop of vaccine (containing 5 mg. of BCG per 1 cc.) thirty firm tangential punctures were made with a needle. Each animal was thus scarified twice, once on each side of the vertebrae. The animals were skin tested at regular intervals with Old Tuberculin (0.2 cc. of a 1:10 dilution and later with 0.1 cc.).

Results: Table 1 gives the results of twenty-four animals. The significant feature is that 58.3 per cent of the animals reacted to tuberculin after one week and 100 per cent are still positive after twenty-four months (animals still alive). In another but smaller series of animals sensitivity to tuberculin is still manifest after three years.

In order to determine the rapidity by which the microörganisms are absorbed, if at all, a similar procedure as above was carried out for vaccination but the skin and subcutaneous tissue and fat were removed for a wide area about and including the injected site. These sites were removed at intervals varying from five minutes to ten days. The animals were skin tested with Old Tuberculin as above (Mantoux method).

Results: Positive results were obtained in all cases, but the time element differed. Thus if the skin was removed before two hours had elapsed, about three months were required before sensitivity to tuberculin occurred; if it was removed after twenty-four hours tuberculin sensitivity developed after one week. These animals are still alive and continue to react to Old Tuberculin after sixteen months.

Grossly there were no visible lesions except for the scabs produced at the scarified points. No visible scars resulted. The lymph nodes were not grossly palpable but were found enlarged when dissected out.

Microscopical studies: Typical tubercles developed at the junction of the epidermis and cutis and in the cutis proper (a detailed microscopical study will be reported in another communication).

Of great significance was the condition of the cutaneous and subcutaneous lymphatics soon after inoculation (one to five hours). Following the multiple puncture method the lymphatics contained a few polymorphonuclear leucocytes which had phagocytosed tubercle bacilli. On the other hand, following a large single intracutaneous dose, the lymphatics were widely dilated and stuffed with cells and bacteria—amounting to a partial obstruction.

Discussion of experimental results: The method of multiple punctures as described fulfills all of the criteria mentioned above.

For a better understanding of why a small dose of bacilli may yield as good or better results than larger doses, a histological comparison of this method and the regular single intracutaneous method is enlightening. In the former there were multiple foci of minute quantities of bacilli, which called forth tissue responses that were accompanied by good drainage by the way of patent lymph channels. Following a single intracutaneous inoculation of the same or larger amounts of vaccine there was only one local lesion which, because of the massive concentrated dose of bacilli, caused local tissue destruction that was further enhanced by the partial blockade of the lymph channels. This blockade hinders the body from experiencing the full effect of the vaccination.

That absorption of the bacilli occurs with great rapidity is shown by the positive tuberculin skin reactions obtained after the removal of the injected sites at varying intervals. Hudach and McMaster have shown by the use of dyes that minute quantities of dye injected intracutaneously are rapidly absorbed by way of the lymphatics. Nègre, Balteanu, Toma and Garogulo have demonstrated in animals, including the chimpanzee, that multiple small doses are superior to one large dose of the vaccine in protecting these animals against virulent tubercle bacilli. They used intracutaneous, subcutaneous and intravenous routes, injecting by means of a syringe and needle.

Because the experimental results indicated that the multiple puncture method of vaccination was a superior one, a clinical series was begun.

Clinical studies: After three years of uninterrupted study with a culture of BCG obtained at the Pasteur Institute from Doctor Guérin, and after proving its harmlessness in about 800 guinea pigs and rabbits, vaccines were made by the exact method used at the Pasteur Institute in Paris.

The infants included in this report were all in the Cook County Hospital. Only those in an environment free of tuberculosis were accepted. This was determined by physical examination and X-ray films of the mother and the entire household. Vaccination was performed on the fifth to seventh day of life. The following methods were employed:

1: *Multiple puncture:* This consisted of thirty-five tangential needle pressures through a drop of vaccine (1 cc. = 5 mg. of BCG) applied to the lateral aspect of the left arm (approximate dose: 600,000 bacilli).

No visible local reaction or definitely palpable lymph nodes were noted. Pinpoint to pinhead sized scars were at times seen after three months.

2: *Intracutaneous injection:* The vaccine was injected in 0.1 cc. amounts (approximately 1,500,000 bacilli or 0.038 mg.) into the skin of the lateral aspect of the left arm.

A local nodule (5 to 8 mm.) formed after three to five weeks which was either evacuated or completely absorbed. Lymph nodes were occasionally palpable. There was no general reaction in either method of vaccination.

3: *Controls:* These received no vaccine but were seen and tested with tuberculin exactly like the vaccinated group.

Results of the Mantoux test: (table 2). The infants were sent home with their mothers at the regular time, that is, eight days after delivery. They were seen at home monthly by a visiting nurse and returned to the clinic after three months and after one year at which time they

were tested with Old Tuberculin. The three month old infants were injected intracutaneously with 0.1 cc. of a 1:1000 Old Tuberculin and the one year olds with 0.1 cc. of a 1:500 dilution. The readings were taken at forty-eight hours.

As seen in table 2 the results, with one exception, were uniformly positive. Of the scarification group two cases were revaccinated and of the intracutaneous, one case. This occurred early in the experiment before the technique was well established. All vaccinated cases tested with

TABLE 2

Results of BCG vaccination in infants

Number of cases under observation	467
Number of vaccinations	235
A. By multiple puncture	133
B. By intracutaneous injection	102
Number of controls	232
Number of Mantoux tests	448

RESULTS AFTER 3 MONTHS*	NUMBER	PER CENT POSITIVE
A. Multiple puncture	97	99
B. Intracutaneous	64	98.4
C. Controls	154	0

RESULTS AFTER ONE YEAR	NUMBER	PER CENT POSITIVE
A. Multiple puncture	30	100
B. Intracutaneous	25	100
C. Controls	46	2.2†

* In 26 cases skin tested with 0.1 mg. of OT between the ages of two and seven weeks, in the multiple puncture group, 66 per cent were positive at two weeks, 92 per cent at three weeks and 100 per cent at four to seven weeks; in the intracutaneous group none was positive at two weeks and 100 per cent were positive at three to seven weeks.

† The one positive case has an active tuberculosis and is now hospitalized.

tuberculin three months after vaccination reacted with moderate severity (average is 15 x 15 mm. with well established redness and induration, a two-plus reaction).

Condition of children: The children are in good health and no ill effects have been noted from the vaccine. The mothers were apprehensive of the suppurating lesion that occurs after the single intracutaneous method of inoculation, but there was no systemic effect accompanying this lesion. One infant of the vaccinated group (multiple puncture)

died at six weeks of age and one of the control group died at eight weeks. They were both autopsied. The former died of an infectious diarrhoea without evidence of tuberculosis, grossly or microscopically. The control infant died of a septic meningitis and a pyaemia (*Staphylococcus aureus*). One infant of the control group has developed active tuberculosis.

Discussion of clinical results: The results obtained by the multiple puncture and the intracutaneous methods are similar as far as the response to tuberculin is concerned, all reacting positively at this time. In the former, however, only one-third the number of bacilli at most was used, there was no suppuration and the syringe and injecting needle were not necessary. (The vaccine can be put up in a capillary tube and a plain sewing needle in another tube similar to the packing of the vaccinia virus.)

Park and Kereszturi report that only when suppuration of local lymph nodes occurs do 100 per cent of the infants vaccinated react to Old Tuberculin. Wallgren obtained 93 per cent positive results in six weeks but 8 of 35 had to be revaccinated, some several times. Similar results have been reported by numerous workers (see literature by Kayne).

SUMMARY

1. Vaccination with BCG by the multiple puncture method has yielded 99 to 100 per cent positive skin reactions to Old Tuberculin in infants in an environment free of tuberculosis, tested three months and one year following vaccination. Control infants did not react to Old Tuberculin (except one case of active tuberculosis).

2. Because the multiple puncture method gives equally as good results as a single intracutaneous injection it is felt that the former is superior because by this method there is (*a*) no gross local lesion, (*b*) no suppuration of lymph nodes, (*c*) no appreciable scar, (*d*) ease in administration and thus wider applicability, and (*e*) smaller dose of vaccine needed.

3. It is believed that larger doses are needed for the single intracutaneous injection than for the multiple puncture method, because a large single dose causes at least partial obstruction of the draining lymphatics which hinders the absorbtion of the vaccine as well as the effects of the tissue response.

BIBLIOGRAPHY

(1) Balteanu, I., Toma, A., and Garogulo, A.: Ann. Inst. Pasteur, 1936, *57*, 152.
(2) Calmette, A., Guérin, C., Boquet, A., and Nègre, L.: La vaccination preventive contre la tuberculose par le "BCG," Paris, Masson et Cie, 1927.
(3) Hudach, S., and McMaster, P. D.: Jour. Exper. Med., 1932, *56*, 223; 1933, *57*, 751.
(4) Kayne, G. G.: Amer. Rev. Tuberc., 1930, *34*, 10.
(5) Kereszturi, C., Rosenberg, H. A., and Park, W. H.: Ibid., 1937, *36*, 90.
(6) Nègre, L.: Compt. rend. Soc. biol., 1934, *114*, 379.
(7) Rosenthal, S. R.: Jour. Dis. Child., 1937, *54*, 296; Arch. Path., 1936, *22*, 348; Ann. Inst. Pasteur, 1937, *58*, 652.
(8) Wallgren, A.: Jour. Amer. Med. Assn., 1928, *91*, 1877.
(9) Weill-Hallé, B., and Turpin, R.: Bull. acad. de méd., 1927, *97*, 126.

EDITORIAL

Biological Abstracts

There is hardly a worker in the broad field of biology who does not feel deeply indebted to *Biological Abstracts*, and hardly one who has not wished at times that it were smaller, more restricted to his own field of interest, thereby more easily handled—and less expensive. *Biological Abstracts*, not supported by any membership fees nor by a permanent fund, has struggled valiantly to keep alive financially and to become independent of financial support. In a recent announcement the Board of Trustees presents a new plan that should provide the individual worker with the kind of abstract journal most suited to his particular needs and financially in easy reach, and that should insure the continuation of *Biological Abstracts* on a sound financial basis.

It is proposed, according to this announcement, that *Biological Abstracts* in its entirety be continued to be published, as heretofore, but that in addition five editions covering only certain constituent parts of the whole be made available to individual subscribers. The proposed grouping is as follows:

(1) *Abstracts of General Biology* to include General Biology, Biography-History, Bibliography, Evolution, Cytology, Genetics, Biometry, and Ecology.

(2) *Abstracts of Experimental Animal Biology* to include Animal Physiology, Nutrition, Pharmacology, Pathology, Anatomy, Embryology, and Animal Production.

(3) *Abstracts of Microbiology and Parasitology* to include Immunology, Bacteriology, Viruses, Parasitology, Protozoology, and Helminthology.

(4) *Abstracts of Plant Sciences* to include Phytopathology, Plant Physiology, Plant Anatomy, Paleobotany, Systematic Botany, Agronomy, Horticulture, Forestry, Pharmacognosy, and Pharmaceutical Botany.

(5) *Abstracts of Animal Sciences* to include Paleozoology, Parasitology, Protozoology and Helminthology, Systematic Zoology, and Economic Entomology.

It is sincerely hoped that a sufficient number of part-subscriptions will be entered so that this plan will be a success, since it would be an irreparable loss to biological workers if *Biological Abstracts* should have to suspend publication.

M. P.

BOOKS

J. E. BANNEN: *The Radiology of Pulmonary Tuberculosis. Pp. vii + 156, with 39 illustrations, Baltimore, William Wood & Company, 1937, fabrikoid, $4.50.*

By F. MAURICE McPHEDRAN

In this book, within a compass of 152 pages of text and illustrations, the author has discussed a wide variety of topics, in nine chapters headed as follows: I. *Technique of Chest Radiography;* II. *The Normal Lung;* III. *General Considerations;* IV. *Pathogenesis of Pulmonary Tuberculosis;* V. *Adult Type;* VI. *Differential Diagnosis;* VII. *The Clinical Aspects of Pulmonary Tuberculosis;* VIII. *Pneumoconiosis;* IX. *Collapse Therapy.*

The author, in his preface, points out that he has "attempted to give a conception of the pathology of pulmonary tuberculosis, which I consider best suits the radiographic picture, and which appeals to me, an outside observer, as the truest conception of this morbid condition amongst the controversies on this subject." The difficulty of such a presentation is that the various observations and conclusions are extremely hard to integrate. To present all of the data necessary for such complex topics as are considered would require considerably more space and larger and more detailed illustrations. The majority of the illustrations measure approximately three and one-half by two and three-fourths inches. This is very much too small a size for the accurate representation of the complex detail of pathological lesions. It is regrettable that illustrations of chest films are so difficult and expensive to make, but those who have worked with reproduction realize that, unless the figures are large enough and are reproduced with full range of contrast and detail, they do not give a clear impression of the lesion, either to the expert or to those who seek merely an outline knowledge of the subject. In these illustrations, specifically, it is impossible in many cases to determine the quality and structure of the shadow. This applies not only to such complex problems as the differential diagnosis of hilum density, including the nodes, but also to the diffuse or scattered and confluent or consolidated lesions of the lung field.

In the text there is a certain "unsharpness" of thought and wording—to use a roentgenological term—and some statements that appear contradictory. These characteristics may arise chiefly from the scheme of the book, as defined by the author and quoted above. They appear especially in discussing the pathogenesis of tuberculous lesions. Any such consideration of this vexed and extremely complex subject must take due account of pathological and

experimental studies, and must be correlated with the well established facts that have emerged from accurate epidemiological studies, and above all from serial roentgenograms showing the evolution of lesions in typical cases at different age periods. For the diagnosis of tuberculosis and for its prognosis single views of lesions are of little value to-day. It is their course and the conditions under which they develop and retrogress that occupy the minds of those interested in the study and treatment of this disease. Some of these considerations are noted by the author, but for the most part they are not thoroughly developed in the text, and they are not reflected in the illustrations.

The author notes the importance of serial films in prognosis, and recognizes the roentgenogram as the sole evidence, the "last court of appeal," before symptoms and signs have developed and after their disappearance. As he rightly says, ". . . no case is healed until serial films have been made over a period of several months. Then only should we use the term arrested."

In so small a space the discussion of technique is naturally limited. The author's points in this section are by long odds the best in the book and are thoroughly sound as far as they go. The author insists on the value of comparable exposures. "Detailed radiographic data should be kept in each case, giving kilovoltage, milliamperage, distance, make of film and centring, otherwise a tuberculous process in subsequent examinations may show an entirely different picture. It is very necessary that serial radiograms should be of the same contrast and density, before a comparison can be made."

GUIDO POLLITZER: *Digrafía. A new radiographic method for the examination of mobile organs. (Spanish) Pp. 104, with 41 illustrations, Imprenta Sebastian de Amorrortu, Buenos Aires, 1937, paper.*

By FRIEDRICH G. KAUTZ

In this monograph the author describes a new method of roentgenological examination of mobile organs which in a simple way might combine the advantages of roentgen-kymography and roentgen-cinematography. While the latter consists of series of consecutive pictures taken on different films by means of a movie camera, roentgen-diagraphy uses only one film which is exposed two or three times through the moving slots of a kymographic grid of special construction. The device described permits only two or three exposures and the author intends to build an equipment that permits up to twelve exposures, the frequent shifts of which are better suited for gastro-intestinal examinations. During the exposures the organ to be examined moves and, according to the shifts of the grid, one-half or one-third of the film is successively exposed. The finished film shows two or three different stages of the movements of the organ. The device consists of two grids, one

for the film to be exposed and the other for demonstration of the movement on the film in the viewing box. The grid of the latter is connected with an electric motor and moves according to the rhythm of the organ studied. The result obtained on the film gives the impression of a mobile organ. Thus the author was able to study various normal and pathological chest conditions. The method, a frozen fluoroscopy, has many advantages when compared with kymography, cinematography and fluoroscopy. Roentgen-cinematography is still an expensive procedure and, therefore, available only in a few places. Fluoroscopy does not exclude errors of subjective interpretation, it is fugacious and not a lasting document. The kymogram does not register other movements than those that are perpendicular with the movement of the grid and therefore its usefulness in thoracic lesions is limited. Furthermore, kymographic pictures are hazy and sometimes distorted, while the pictures obtained by diagraphy are sharp and unobstructed. The author hopes that roentgen diagraphy will prove to be a valuable addition to the examination of problems of respiratory dynamics, in the field of pulmonary physiopathology and especially in pulmonary tuberculosis. Normal and pathological conditions of lungs and bronchi may be studied as well as the results of collapse therapy, of changes of position of the intrathoracic structures, such as mediastinal shift, pleural adhesions and the effect of these lesions on associate pulmonary lesions. The method is well and concisely described and the text is accompanied by numerous photographs of the equipment and by reproductions of roentgen films which attempt to give to the reader the indications and impressions to be hoped for from this method.

E. COULAUD: *Le pneumothorax bilatéral simultané. Pp. 73, G. Doin & Cie, Paris, 1938, paper, 14 Fr.*

By MAX PINNER

In this brief monograph the author discusses clearly, but without much detail, the indications, contraindications, management, complications and results of simultaneous bilateral pneumothorax. The fact that Doctor Coulaud published, in 1930, a report on 116 patients with bilateral pneumothorax (Ann. de méd.) is indicative of his wide experience in this field of therapy, but the reader would probably like to know how many patients Doctor Coulaud has treated since. Throughout this monograph no figures, no statistics are mentioned; certain occurrences are stated to be *très rare* or *assez fréquent*; more definite information would be welcome. This applies particularly to therapeutic results. It is only stated that the late results of bilateral pneumothorax are "evidently infinitely less good" than the immediate results; that, however, at the end of ten years 30 to 35 per cent maintained cures are achieved, while

after two to three years more than 50 per cent favorable results are attained. Doctor Coulaud points out that statistics are easily misleading because they depend to a large extent on the selection of the patients. The physician who, like the author, includes many evidently poor risks will have a relatively low percentage of cures, but he will have the satisfaction of having saved the lives of a few desperately ill patients.

Doctor Coulaud discusses in an interesting way the essentially different prognosis of patients who at the beginning of the treatment had bilateral active disease and those in whom a contralateral spread occurred following a period of unilateral pneumothorax treatment.

Another point of particular interest is the observation that quite a few patients show rapid weight loss following bilateral induction of pneumothorax, evidently dependent on it. This phenomenon is considered of grave significance; its mechanism is not explained.

Throughout the essay the author warns frequently that the management of bilateral pneumothorax is beset with many perils, that it requires minute observation, skill developed by experience and mature judgment.

This monograph is warmly recommended to phthisiologists—it emphasizes wisely the therapeutic potentialities and the limitations and dangers.

JACQUES FRANCILLON: *Le pneumothorax extra-pleural chirurgical. Pp. 172, with 34 illustrations, Librairie Louis Arnette, Paris, 1938, paper.*

By MAX PINNER

The first chapter of this book is a thorough discussion of surgical anatomy of the endothoracic fascia, the areolar tissue of the mediastinum and the surgical applications of these observations. In the second chapter, the operative technique is presented in considerable detail, and due emphasis is placed on the freeing of the mediastinal pleura and the final shape of the extrapleural space. The operative complications and the proper maintenance of the extrapleural space are the subjects of the third chapter. These first three chapters are replete with solid and basic information and should prove of definite value.

The remaining three chapters on indications, case reports and results seem of questionable value because they are based on the limited experience with 17 patients. With the exception of one patient, followed for sixteen months, all of these patients were observed for periods of less than one year following the operation, 10 of these patients were observed for less than six months, and 6 patients, two of whom died, were observed for three months or less. Nevertheless all 17 patients are included in the final paragraph on *Resultats éloignés*. With such inadequate observation periods, reports of results seem rather meaningless, and the basis for indications tenuous. The information pre-

sented in the case reports is superficial, and further doubts of its validity are created by such "observations" as the "perfect cicatrization" of a fairly large cavity, twenty-seven days following the operation.

A valuable addition to the text is a quite extensive bibliography that consists not only of the customary references but of brief abstracts of practically all papers cited.

N. S. Morozovski and B. P. Alexandrovski: *Parahilusnii tuberkulioz u doroslich. Parahilar Tuberculosis in Adults. (Russian) Pp. 139, with 29 illustrations in text, Kiev State Tuberculosis Institute, Derszmedvidav, 1937, USSR, paper, 3krb. 50kop.*

By WILLIAM A. ZAVOD

The monograph is a study of the tuberculous involvement of the parahilar regions of the lungs in adults. The book is written in the Ukrainian language—a tongue intelligible to very few phthisiologists in the United States; fortunately detailed summaries in the Russian and French languages are appended.

The main thesis of the monograph is that tuberculous lymph nodes in the roots of the lungs are not only the source of earliest forms of adult tuberculosis in the parahilar region but also responsible for the early forms of adult tuberculosis in other regions of the lungs. The arrangement of the treatise is in textbook style with chapters on anatomy, pathology, physical signs and symptoms, diagnosis, etc. The authors subdivide hilar tuberculosis into disease of the hilar nodes; tuberculous periadenitis with involvement of the tracheobronchial nodes; and parahilar tuberculosis, the latter being an intrapulmonary process whose substratum is the pulmonary and lymphatic tissues of the mesial lower two-thirds of the lung. The involvement is usually more marked posteriorly since anatomically the roots of the lungs are more posteriorly located. Pathogenetically the fact is stressed that primary tuberculosis of the hilar nodes can arise along a retrograde route by way of the tonsils, cervical nodes, supraclavicular nodes, pleura and finally hilar nodes, sparing the pulmonary parenchyma entirely. Spread from this point can occur along the lymphatic routes, and the mediastinal and interlobar pleurae are frequently involved. Later in adult life open tuberculosis arises from reactivated lymph nodes in the roots of the lungs. Physical signs and symptoms are thoroughly discussed, probably too thoroughly—over three pages having been devoted to the finesse of percussing out a dulled note of the author's triangle posteriorly near the lower thoracic spine. Prognosis is poor in open parahilar tuberculosis and treatment such as pneumothorax, thoracoplasty and phrenicectomy are effective in very few cases. Roentgenograms should be taken in the ventrodorsal position since the earliest forms of parahilar disease are best visualized in this position.

This monograph is an important contribution to the fight against tuberculosis in the Soviet Union, written in simple language and readily understandable by the general practitioner who is urged to look for early adult tuberculosis in the parahilar region, not the apices. However, the purpose served would have been much greater, were the authors to stress early roentgenography, instead of attempting to teach at length diagnosis based on signs and symptoms which are not always reliable criteria even in the hands of experts.

YANDELL HENDERSON: *Adventures in Respiration, Modes of Asphyxiation and Methods of Resuscitation. Pp. 316 + xi, with frontispiece, 15 figures, and 1 illustration in the text, The Williams & Wilkins Company, Baltimore, 1938, cloth, $3.00.*

By AARON EDWIN MARGULIS

Although this book has little practical bearing on clinical phthisiology, except perhaps for the thoracic surgeon, it is heartily recommended to all those busy clinicians who perhaps wistfully regret lack of time to obtain deeper insight into the biochemistry and physiology of respiration by independent bibliographical search. For although the main theme of the book is the problem of asphyxia—its genesis and therapeutic control—it presents a large amount of basic information concerning the respective rôles of the blood, the circulation, and the lungs in respiration, and in so sparkling and vivacious a manner as to make the book excellent bed-time reading. The enthusiasm which carried its author through almost forty years of experimental and clinical investigations along a clearly discerned trail expresses itself on every page in the verve of the telling and the pungency of the style. The lack of a certain modesty of expression, which perhaps unfortunately has come to be expected of scientists turned literateurs, here creates a pleasant impression and perhaps reflects the author's partial heterodoxy. For the prospective reader must be warned that not all of Henderson's theoretical concepts are universally accepted, although their practical applications have been brilliantly successful.

RICHARD M. BURKE: *A Historical Chronology of Tuberculosis. Pp. viii + 84, Charles C. Thomas, Springfield, Illinois, 1938, cloth, $1.50.*

By MAX PINNER

Doctor Burke has made a valiant attempt to recount in the shortest possible manner, using telegraphic style, the essential steps that have led to the present knowledge of tuberculosis. Starting around 5000 B.C. and ending with 1937

the "pertinent records of individuals, discoveries and events contributing most greatly to the story of tuberculosis" are chronologically enumerated in the narrow space of sixty pages in small format. This, indeed, is a formidable task, not only and not mainly because of the wealth of material, but more so on account of the extreme brevity that was aimed at. This necessitated, of course, an exquisitely rigorous differentiation between fundamental and incidental data. The centuries up to and including the discovery of the tubercle bacillus stand out in clear historical perspective due to the sifting work of Waldenburg, Predöhl, Neuburger, Pagel, Garrison, Webb and many other authors who have analyzed specific fields in the history of tuberculosis, and due eminently to the fact that the passage of time has shown which building stones were basically important and which were not. When it comes, however, to what may be broadly termed the contemporary period, selection becomes mainly a matter of individual judgment. I believe that hardly two observers could agree upon the entire selection and omission of data since 1882. The data covering the last fifty years could easily give rise to a number of disputations on priority claims.

Who can say whether the four books that are mentioned within the last twenty years are historically more important than any not mentioned? Some may criticize the omission of apparently significant epidemiological work, others that of basic pathological studies. *Nomina sunt odiosa*; but in a brief conversation with other men in the field of tuberculosis, we agreed on approximately a dozen names, not included in Doctor Burke's list, that seemed more important than some mentioned during the last fifty years.

In a later edition, the addition of a complete bibliography of all the discoveries and developments mentioned would increase enormously the value of this book. As it stands now, it should not be used as an introduction to the history of tuberculosis, nor as a textbook. Its real value is for the man, basically familiar with the subject, who wants to reascertain some historical detail or recall the exact date of a given fact or refresh his memory on some sequence of events.

The extreme conciseness of this book is both its greatest virtue and its most imminent potential danger—at least for those who should not use it; for it is not to be recommended for the tyro, but, and warmly so, for the reader with a critical knowledge.

Brief Comment

M. JAQUEROD: *Le traitement de la tuberculose pulmonaire par la tuberculine. Pp. 43, with 4 illustrations, Librairie Payot & Cie, Lausanne, 1937, paper.* A broad, general, extremely simple and not very informative discussion that

is based on the author's experience since 1903. His indications and contra-indications are quite cautious; his results, that are claimed but not presented, appear encouraging but far from spectacular.

JACQUES STEPHANI: *Sémiologie radiographique pulmonaire. 2nd edition. Pp. 129, with 155 illustrations, G. Doin & Cie, Paris, 1938, paper, 50 Fr.*
Although not stated in the title, the book is limited to pulmonary tuberculosis. The basic roentgenological alterations are well presented and illustrated, not by photographs from roentgenograms but by line drawings. These drawings may prove to be a successful teaching tool in the interpretation of chest roentgenograms.

NOËL RIST: *L'Allergie conférée par les bacilles tuberculeux morts enrobés dans les paraffines. Pp. 161, with 15 illustrations, Paris, Librairie E. le François, 1938, paper.*
A thorough discussion of the pathological and immunological consequences following the injection of oily suspensions into guinea pigs. The immunity conferred by such inoculations is stated to be about equal to that produced by BCG vaccination.

EDMUND JACOBSON: *You Can Sleep Well. Pp. 269, with 40 illustrations, Whittlesey House, McGraw-Hill Book Company, New York, 1938, fabrikoid, $2.00.*
The author of *Progressive Relaxation* presents for popular consumption, in easily readable and entertaining style, the practical application of his physiological investigations to the problem of insomnia. It would seem that full relaxation of tension, according to the author the prerequisite of sound sleep, must be developed by intense and strenuous efforts.

Books Received

RODOLFO CUCCHIANI ACEVEDO: La duración de la colapsoterapia gaseosa y el problema de su interrupción. Tesis de doctorado, Universidad Nacional de Buenos Aires, Facultad de Ciencias Medicas. Pp. 64, 1938, paper.

Birth, Stillbirth, and Infant Mortality Statistics, 1935, Twenty-first Annual Report. Prepared under the supervision of Dr. Halbert L. Dunn, Chief Statistician for Vital Statistics. Pp. 207, U. S. Department of Commerce, Bureau of the Census, United States Government Printing Office, Washington, 1937, buckram, $1.25.

Brompton Hospital Reports. A collection of papers recently published from the Hospital, Volume VI. Pp. 183, Gale & Polden, Ltd., Aldershot, 1937, fabrikoid, 2s. 6d.

Conferências da Ligo Portuguesa de Profilaxia Social. Pp. 355, Imprensa Portuguesa, Pôrto, 1935, paper.

JOSEPH HOLLÓS: Immune-Blood Therapy of Tuberculosis. Pp. 197, New York, 1938, cloth.

ERIC M. MATSNER: The Technique of Contraception. With a foreword by Frederick C. Holden. Pp. 50, with 25 illustrations, 1938, Williams & Wilkins Company, Baltimore, published for the National Medical Council on Birth Control, paper.

Mortality Statistics, 1935, Thirty-sixth Annual Report. Prepared under the supervision of Dr. Halbert L. Dunn, Chief Statistician for Vital Statistics. Pp. 364, U. S. Department of Commerce, Bureau of the Census, United States Government Printing Office, Washington, 1937, buckram, $1.50.

GEORGE W. NORRIS AND H. R. M. LANDIS: Diseases of the Chest and the Principles of Physical Diagnosis. Sixth Edition, Revised. Pp. 1019, with 478 illustrations, Philadelphia and London, W. B. Saunders Company, 1938, cloth, $10.00.

Papworth, The Sims-Woodhead Memorial Laboratory, Research Bulletin for 1937. Pp. 200, Papworth: Pendragon Press, 1938, paper.

Tisiologia quinto curso de perfeccionamiento. Director: Prof. Dr. G. Sayago with 13 collaborators. Pp. 353, with many illustrations, Imprenta de la Universidad, Cordoba (Rep. Argentina), 1938, paper.

KARL URBAN: Die Chirurgie des Kropfes. Pp. viii + 112, with 51 illustrations, Leipzig and Wien, Franz Deuticke, 1938, paper, Mk. 7.

C. W. WELLS AND H. H. SMITH: The Epidemiology of Tuberculosis in Kingston, Jamaica, B. W. I. Pp. 71, Jamaica Government Printing Office, Kingston, 1938, paper.

LATE RESULTS OF THORACOPLASTY

An Evaluation of Results from Fourteen American Clinics in 1,636 Cases

FRANK S. DOLLEY,[1] JOHN C. JONES[1] AND JOHN R. PAXTON[2]

Low surgical mortality, marked reduction in sputum, and a delightfully foreshortened sanatorium course have led chest specialists and tuberculous patients alike to conclude that the former need have no hesitancy in advising, nor the latter in accepting, thoracoplasty as a reasonably sure shortcut back to health. As our own individual series of thoracoplastic cases mounts we are learning, with more and more disquieting frequency, of patients one, two or three years after thoracoplasty, whom we have presumed to be comparatively well and probably working, who are actually still invalids. Their sputum has again become positive; they fatigue so easily that steady work is not possible or chest-wall pain precludes rest and so recovery. What actually are the end results for the people on whom thoracoplasties have been done? How many are dead? How many are still sick? How much have they really improved? How many are actually leading reasonably happy contented lives and are at work without pain, positive sputum or dangerous fatigue?

A questionnaire was sent to every member of the American Association for Thoracic Surgery who is treating pulmonary tuberculosis. This group by no means includes all the surgeons who are doing excellent thoracic surgery and but a very small number of the competent phthisiologists in this country, yet it comprises a sufficient number to provide a reliable foundation for judgment from their combined cases concerning our end results following thoracoplasty.

A high percentage of replies was received. Yet startlingly few had thoroughly reviewed their older cases. Many are just getting to an extensive check-up, even as we are by this paper. The stress of their own work made it impossible to undertake quickly this extra time-consuming *Arbeit*. The critical review of American thoracoplastic end results that follows is based upon 1,386 cases plus 250 of our own. While

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it represents but a comparatively small proportion of all those done in this country during the past five years, yet, with the reliability of the figures and the excellence of the operators evident, it provides us with a reasonably accurate conception of how well or poorly we are guiding our patients by thoracoplasty back to health, and what we should strive to do in order to reduce or eliminate those operative or postoperative factors of omission or commission that preclude so called permanent arrest of pulmonary tuberculous disease. The statistics we have been enabled to collect from the surgeons whose results appear in this publication are based entirely on personal communications and have not heretofore appeared in the literature.

The minimal period of observation following thoracoplasty has been established in this paper at two years. Where the authors have found certain cases to have had a postoperative course shorter than that, they have not been included in end-result tables. Certain apparent discrepancies can be thus accounted for. Unfortunately there could be found no certain way to check with all contributors concerning the percentage of cases lost in the follow-up. In our series it was 10.7 per cent. Probably this constitutes an approximate average for the combined cases. Because of this unknown group and because the results appearing in this report are from among the most experienced clinics in the country, the statistics shown are probably peak performances and, were the patients lost in the follow-up to be found, would be better perhaps than they, including the authors, have really obtained. Moreover, unmodified statistics at their best contain so many variables as to make conclusions based entirely upon them unreliable, and they are probably at their worst when based upon thoracoplastic results. The technique and judgment of the surgeon and his medical associates, the type and extent of pulmonary involvement of the patient treated, and the degree of chest-wall and lung collapse vary much with different men. No two clinics follow identical courses. Moreover, every year, indeed every month, some change is made in all busy centres where many thoracoplasties are done that, it is hoped, will bring about improvement in end results. It is neither truthful nor fair to compare the successes or failures of the men who risk unfavorable statistics in their desire to bring relief by thoracoplasty to those whose chances for eventual arrest are forlorn, with the figures of those surgeons who refuse aid to all but good chronics and whose constant objective, apparently, is the compilation of statistics suggesting superlative surgical skill. In the consideration of the various aspects of

this subject, therefore, only those figures felt by the writers definitely to convey conclusions of dependable importance will be quoted. Fortunately, much valuable information can be obtained in this manner.

In the discussion of many phases of the patient's progress both during his thoracoplastic course and subsequent to it, it is absolutely essential that the exact methods employed be stated in order that the reason for the fortunate or unfortunate result may be clear. It has therefore seemed expedient a number of times in this study to refer specifically to our own cases in order to render definite the particular point requiring emphasis. We refer particularly to the procedures employed in obtaining complete cavity closure and in minimizing persistent chest and shoulder pain and deformity.

The following collected statistics on thoracoplasty are based on that type of operation where there was complete removal of the upper one, two or three ribs with the extensive resections of those below. It seems uniformly agreed that the end results have markedly improved since this type of operation has been adopted. The total number of cases collected for this paper is 1,636, of which 640 were complete thoracoplasties, that is, the excision more or less extensive of eight or more rib sections, 839 partial thoracoplasties where seven or less rib sections were removed.

The total removal of the upper four ribs to the cartilages with extensive resection of the fifth and sixth, often including their corresponding transverse processes, not only causes surprisingly little visible change in the contour of the chest-wall but also produces no great reduction in the vital capacity appreciable to the patient. It is seldom indeed that disaster follows the first stage where the upper three ribs are completely removed. While often there is a considerable collapse and, indeed, pressure against this portion of the lung deprived of its ribs yet actually the number of cubic inches affected is comparatively small at the apex where this organ is narrowest in all dimensions. Nor, for the same reason, is there ever great paradoxical motion following this stage. After the removal of the fourth and fifth ribs, however—and with most men this constitutes the second stage—paradoxical motion often becomes marked, even dangerously so. If further rib resection is postponed for another stage, then the temporary reduction in the vital capacity of the patient rarely becomes disastrous. Often in partial thoracoplasty only these upper five ribs are excised. If it is necessary to remove the sixth rib, this represents the third stage provided only the upper six are to be removed. A section of the lower end of the scapula is excised to permit

the latter to drop in flatly against the lung and, at the same time, clear the mesial surface of the seventh rib in abduction and adduction of the upper extremity. The patient in the meantime has had an opportunity for stiffening of the chest-wall so that, even though paradoxical motion was considerable following the second stage, extensive resection of the sixth rib does not materially increase it.

In the collected series there have been 839 partial thoracoplasties; 566 faced complete and probably permanent invalidism without thoracoplasty; 59 were able to work part time even though sputum-positive; 350 had a productively fibrotic process in the contralateral lung; 355 showed the opposite lung apparently free. From two to five years after

TABLE 1

	TOTAL THORACOPLASTIES	PARTIAL THORACOPLASTY	COMPLETE THORACOPLASTY
Eloesser	205	134	71
Urquhart	200	41	159
E. C. Janes	64	47	17
Decker	59	14	45
R. M. Janes	120	62	58
Freedlander	85	Not separated	
Eggers	34	28	6
Raine and Yates	56	Not separated	
Gale	155	53	86
Thearle	45	34	11
Moore	30	20	10
Peters and Cornish	38	38	0
Overholt	295	223	72
Dolley-Jones-Paxton	250	145	105
Total	1,636	839	640

partial thoracoplasty 241 out of 596 have persistently negative sputum by concentration and are able to work. One hundred and thirty are improved, that is, they have occasional positive sputum and are able to do some work. Sixty-eight out of 453 are unimproved, that is, the sputum is usually positive and their condition for enjoyment of life no better than before thoracoplasty. Out of 616, 85 died within eight weeks following partial thoracoplasty, 9 within six months, 9 within one year, 7 within two years and 3 within five years. Thus out of 616, 85 died in the first eight weeks and 28 in the next four and one-half years.

The total number of complete thoracoplasties, that is, eight or more ribs, was 640. Three hundred and forty-four had little or no hope of

anything but complete invalidism without thoracoplasty. Forty-five were able to do some work even though their sputum was occasionally positive. Two hundred and seventeen had a productively fibrotic process in the contralateral lung. Two hundred and sixty-four showed the opposite lung apparently clear. After two to five years, 260 showed persistently negative sputum by concentration and were able to do a day's work. One hundred and thirty-one were improved and able to do some work. Thirty-one were unimproved, that is, they still remained bed patients with little hope for improvement. Thirty-four died during the first eight weeks, 10 within six months, 4 within one year, 12 within two years and 3 within five years. Thus out of 640, 34 died in the first eight weeks and 29 in the next four and one-half years.

To the causes of death not enough consideration has been given. Eloesser reported 2 cardiac deaths, Urquhart 9, and Peters 13; Overholt 15 late deaths from spread of the disease, Urquhart 5, and Moore 2. A careful scrutiny of those complications that terminated in death in our series of 250 cases reveals the startling fact that many catastrophies clearly could have been averted.

Of our 16 deaths less than eight weeks following thoracoplasty, none died from shock, 4 from atelectasis, 3 from mediastinal pendulation with paradoxical respiration on the operated side with cardiac failure, 2 from pulmonary stenosis or atresia causing retention of infected material within a collapsed lobe, 2 from acute gastric dilatation, 1 from uraemia.

In any considerable series, disaster secondary to any one of the above mentioned causes of death is inevitable despite every known precaution that is taken to prevent its occurrence, yet a critical consideration of the causes of death will result in reduction with future cases.

Shock in these days of multiple stages seldom results fatally. Indeed, it is uncommon for it to be present even in moderate degree. In the present day procedure of extensive rib resection, the first stage is almost always limited to the complete removal of the upper three ribs, the second stage to the fourth and fifth, the third to the sixth alone or the sixth and seventh. Provided there is not undue haemorrhage, shock will not occur following these limited stages, and, for reasons which will be discussed under immediately following headings, the stages should be thus limited.

Massive pulmonary atelectasis following thoracoplasty may cause death. The percentage of lung engaged in oxygen carbon dioxide interchange is reduced to a greater or lesser degree by tuberculous involve-

ment. Increased toxicity incident upon compression of diseased lung following thoracoplasty demands additional oxygen. Paradoxical motion of that portion of the chest-wall just deprived of its supporting ribs further decreases the vital capacity. The increased negative intrathoracic pressure produced by each inspiratory act is partially satisfied by this paradoxical sucking-in of the chest-wall to the proportionate decrease in the air aspirated by way of the trachea to the pulmonary alveoli. Complete and sudden collapse of another lobe or lobes in atelectasis may so decrease the oxygen supply that death from anoxaemia may occur almost at once or within a few hours. So it is vitally important that every precaution be taken to prevent atelectasis; that should it develop the symptoms of its existence be promptly recognized; that, if ordinary measures do not bring relief at once, catheterization of the occluded bronchus or bronchoscopic drainage be done. The violent inspiratory and expiratory efforts accompanying this procedure may promptly free the obstructed air way.

We are convinced that one of the most frequent causes for post-thoracoplastic atelectasis is painful inspiration. To avoid this pain the patient takes as shallow inspirations as possible, depending for oxygen upon rapidity rather than depth of respiration. Little air enters or leaves his lower lobes. Thus they may be to a great extent excluded from respiration. Mucus collects within their bronchi, occlusion occurs and soon airlessness. In anticipating this, not only is carbon dioxide given every two hours for the first three days following each stage in thoracoplasty so that the patient takes three or four deep inspirations, but also at three or four hourly intervals he is given pantopon, dilaudid or codeine if pain exists, in order to relieve the respiratory distress sufficiently so that upon our insistence he strongly fills his lower lobes frequently with air. He is turned from side to side every three hours and induced to cough that he may aerate these lobes and also get rid of any mucus or infected material that might lead to atelectasis or bronchogenic spread of his tuberculous infection. Nurses are instructed to consider it an emergency demanding immediate notification of the doctor if a patient suddenly develops pain in his chest with dyspnoea. With the development of atelectasis, even more insistence on coughing and carbon dioxide inhalations are energetically resorted to. If benefit is not soon evident, bronchial catheterization or bronchoscopy is at once done. We feel that controlling painful respiration has probably considerably reduced post-operative atelectasis.

Excessively large amounts of preoperative sedatives and too deep and prolonged operative anaesthesia, too frequently repeated postoperative analgesics may reach the other extreme, which is fully as liable to produce atelectasis. For many hours, perhaps, no deep inspiration is taken, no cough occurs. The patient should be very drowsy but not deeply unconscious either before or after surgery.

Mediastinal pendulation, of which paradoxical chest motion is external evidence, is perhaps the most frequent cause of heart failure. If there is a cavity near the mediastinum, large or small, with comparatively clear peripheral lung tissue, we can be sure that extensive removal of three of the lower ribs, particularly the fourth, fifth and sixth, would result in dangerous, even fatal, paradoxical motion and mediastinal pendulation. If, on the other hand, the lung is extensively involved over the area beneath these ribs and the parietal pleura is thickened and stiff, we are equally confident that little pendulation would occur were all three of these ribs completely resected. In four out of five cases, it would be safe in this second stage to remove entirely all three ribs, yet in the fifth case death would follow, not from mediastinal pendulation alone, not from shock which, however, would definitely exist for a few hours, not entirely from autotuberculinization which develops following the chest-wall collapse and the pressure against the infected tuberculous tissue within the lung, but from the combination of all these factors. The marked paradoxical motion following extensive resection of the fourth and fifth ribs is more than doubled by the additional removal of a long section of the sixth. In the fifth case, then, this unnecessary extra load demanded of the patient during the first few postoperative days will prove too great. An extra operation for every one of these five patients is better than a death for one of them through the resection of one rib too many. In the past this has constituted one of the most frequent causes of avoidable disaster. The recognition of its danger will reduce our present day mortality figure.

The excision of regenerated ribs and soft tissue scar over the upper postthoracoplastic chest-wall collapse following prolonged delay between stages, has produced an additional opportunity for serious paradoxical breathing. This will be considered somewhat later in this paper.

As far as the authors are aware there are no known clinical or laboratory procedures that can give us any adequate knowledge concerning the ability of the walls of the heart to withstand sudden increase of resistance to their output. We do know, however, that a patient, many months or

even years at complete bed-rest, particularly if through forced feeding he is markedly above his normal weight, is a poor cardiac risk. Such patients, we insist, should be up in a chair daily for several weeks before thoracoplasty is begun. Repeatedly we have found that they were unable even to stand this extra cardiac exertion. Thoracoplasty would have proved fatal. The other important measure in avoiding cardiac failure is again the limitation of rib removals to two or occasionally two and one-half ribs with each stage below the first one. Two of our three deaths from cardiac failure were probably due to the removal of one rib too many.

Bronchial ulceration with resultant stenosis or atresia is now appreciated as being a comparatively common and usually serious complication of pulmonary tuberculosis. This condition, so splendidly described by Eloesser, is having a fundamental influence upon our interpretation of the various symptoms that occur during the course of this disease. We have known for some years that patients with dyspnoea before thoracoplasty uniformly were bad risks. They were not improved, were made worse, or died following extensive rib resections. The reason for this was not clear. We simply knew that they did not do well and after several disasters refused to operate on others similarly affected.

The symptoms suggesting serious interference with bronchial drainage are usually not difficult to recognize and should at once postpone all thought of thoracoplasty until definite knowledge is obtained concerning the adequacy of drainage from the pulmonary lobe proposed for collapse.

With these patients, cough is harassing and productive only after considerable effort. The sputum is viscid, tenacious and mixed with mucus. Dyspnoea on exertion is greater than can be accounted for by examination with stethoscope and X-ray. Often there are attacks of so called asthma that began only after the onset of active tuberculosis. Cavities are evident by X-ray that may vary greatly in size from month to month, often disappearing entirely for weeks only to reappear with shocking suddenness and without apparent cause.

All these symptoms and signs point to interference with bronchial drainage secondary to scar tissue contraction from healed bronchial ulcerations. Thoracoplasty is ill-advised on such patients unless by bronchoscopy satisfactory evidence is obtained that the main bronchi are patent and draining, for in such patients the very extensive rib resections of the modern thoracoplasty are usually disastrous. With proper appreciation therefore of the symptoms suggesting bronchial

ulceration and stenosis, the deaths from this cause following thoracoplasty should be appreciably reduced. A review of your unimproved thoracoplastic patients and ours will show many who, because of bronchial stenosis, should never have had chest-wall collapse. If dilatation of the stenosed bronchi cannot be accomplished, thoracoplasty probably will not materially improve them.

In our series there were two fatalities, proved at autopsy as due to acute gastric dilatation neither recognized nor considered before death. One died almost without warning while being returned to bed following the first or upper stage rib resection. The other, fourteen hours after the third stage. Both were left-sided thoracoplasties. This complication was discovered only at postmortem examination. How many others throughout the country without autopsy evidence pass unrecognized, with their deaths attributed to acute cardiac failure or embolism?

When temperature goes down and pulse very rapidly goes up with evidence of shock out of all proportion to the extent of surgical trauma, whether it be immediately following a thoracoplastic stage or after the expiration of several days, the possibility of acute gastric dilatation should be at once considered.

One patient died from uraemia eleven days following thoracoplasty. A routine determination of nonprotein nitrogen now excludes those whose kidney function is manifestly too low to permit their carrying an appreciable, even though temporary, increase to their heavy toxic burden.

In the collected series of 1,636 cases, the sputum still continues occasionally or constantly positive in 396. Provided there is no activity in the contralateral lung, there are two probable causes for the continued presence of tubercle bacilli in the sputum: (*1*) incomplete approximation of cavity walls; (*2*) active bronchial or tracheal ulceration.

It is vastly important that we critically consider these improved and unimproved cases. Cavities may persist because of (*a*) too long delay between stages, (*b*) posterior cavities protected by transverse processes which were not excised, (*c*) anterior cavities sheltered beneath costal cartilages which were not removed, (*d*) insufficient lengths of ribs resected so that central cavities from behind forward were at their anterior extremities still held out by lengths of ribs not excised, or (*e*) insufficient ribs removed so that a roughly triangular portion of the cavity wall with its base below could not collapse due to scar tissue anchored to unremoved ribs distal to it.

If for any one or more of these reasons the primary series of operations

was roentgenologically not completely successful, a secondary thoracoplasty eventually had to be done to bring about arrest of the tuberculous process and elimination of tubercle bacilli from the sputum. We have found this secondary operation to be much more dangerous to life than the primary thoracoplasty.

It is essential to recovery that the periods between stages be sufficiently prolonged so that the patient be in approximately as good condition for his next stage as he was before surgery was begun. Often, for some reason, it is necessary to wait two or even three months before proceeding with another stage. Until recently this delay seriously endangered the success of the entire series of operations. This hazard has been in a large measure removed by resorting to the following procedure: The wound is reopened, let us say, for the second stage following the complete removal of the upper three ribs two months previously. The fourth rib is excised with the corresponding transverse process, to its cartilage. This gives a free clear space below the scar tissue and the imbedded partially regenerated ribs above. The scar tissue is freed from the stumps of the transverse processes of the third and second ribs. The third intercostal bundle, situated at the junction of the first and second procedures, is excised including the partially regenerated rib down to the parietal pleura. The second intercostal bundle is then removed together with whatever rib regeneration may have occurred. This is carried through to the cartilages. It is surprising how the removal of these tissues will freshen a previous apparently solid mass of scar tissue that showed no tendency to move with respiration nor to retract further.

It is at this point that caution must be observed that, in the desire to advance with the chest-wall collapse, the paradoxical motion of the thorax deprived of its supports does not become too great. When properly freed from regenerated ribs and scar tissue, the floor of the first thoracoplasty may be nearly as mobile as at the primary removal of the first three ribs. Now the fourth has been perhaps completely removed. The flapping of the lung is considerable and will during the following few days become more pronounced. Wide excision of an additional rib at this time might mean death from anoxaemia, cardiac failure or, with expectoration seriously interfered with, spread of the infection or the development of tuberculous pneumonia. The secondary excision of scar tissue is not easily borne by the patient. It is often much safer to content oneself with the removal of but one extra rib with perhaps a short posterior section of the fifth. The aim has been achieved; the apex

has been again freed and further collapse obtained below it. The danger from long delay between stages has been obviated.

The removal of the transverse processes with the corresponding ribs is of great importance. When a stage is finished the lung still domes in its centre, from behind forward, several centimetres above the level of the transverse processes. It would seem, therefore, of little benefit to excise these transverse processes in the hope of getting a more extensive collapse of the lung in the gutter, since the dome stands up so high. Yet at the next stage when the collapse of the previous one is reviewed, it is found that the pulmonary dome has disappeared and that the lung goes almost straight forward from the top of the transverse processes to the anterior rib stumps. It is, therefore, essential in cavities whose mesial walls are close to the mediastinum, or are going to fall into this position after rib resections, that the transverse processes be excised. It is now almost the routine procedure in most clinics to do so. Many secondary thoracoplasties for incomplete cavity obliteration are thus avoided.

Even to-day it is not generally appreciated that it is important to carry the line of collapse by rib removal as nearly straight across from the spine to the sternum as possible. A cavity, for example, appears in the X-ray six centimetres long in its perpendicular diameter. It is entirely probable that it has an approximately equal horizontal diameter, and therefore while it may seem to be posteriorly located its anterior wall may be two-thirds of the way to the costochondral junctions. Even though the upper four ribs be completely removed with their transverse processes, if considerable distal sections are left of the fifth and sixth ribs, it is more likely than not that an anterior narrow triangular portion of this cavity will be held open by these distal remaining rib ends. An X-ray film taken in the posteroanterior position will often fail to disclose this cavity due to the fact that it rises directly in front of the more or less solidly collapsed tissue from the thickened and obliterated cavity walls immediately behind it. It is highly important to check, previous to thoracoplasty, under the fluoroscope, by turning the patient in oblique positions, as to the probable location of the anterior wall of the cavity or cavities and as to the extent forward the rib resections must be carried in order to obtain the closure of this anterior cavity triangle. Overexposed, even Bucky stereoscopic films are most reliable in case there be doubt. Where cavities are centrally located, lung collapse should be

made to go forward as directly as possible from transverse processes to cartilages or even to sternum.

After the completion of a partial posterior thoracoplasty but before telling the patient that his thoracoplastic episode is closed, very careful consideration should be given to the possibility that the upper three or four cartilages and the anterior stumps of the ribs immediately below may be protecting a partially collapsed cavity or cavities beneath. If there is any question concerning this, an anterolateral thoracoplasty should be carried out. The removal of these anterior stumps is attended with no shock and the procedure itself may be the deciding one between a completely successful and a partially successful collapse of a tuberculous lung.

It is by no means uncommon that thoracoplasty has been stopped just one rib too short. The chest-wall does not fall straight in above the unresected ribs no matter how extensively these ribs have been removed. The line into the collapsed lung is an oblique one and it is by no means rare that the lowest portion of the cavity intended for collapse is held open by the pull of the unresected rib immediately below. Cavities uniformly go downward and inward toward the level of the hilum as the upper ribs are resected. Therefore, it is unsafe to decide before thoracoplasty is undertaken the total number of ribs that are to be removed. It is the usual practice following every stage to take a film for lung detail and a film for spine detail; the former to disclose any evidence of extension of the tuberculous process following thoracoplasty, the latter to bring in view whatever cavities may still be present. We wait at least twelve days in order that the oedema in the soft tissues following the thoracoplasty may not obscure the lung condition beneath.

If, when the thoracoplasty is completed, the sputum is still occasionally or uniformly positive and careful study of stereoscopic X-ray films, taken with spine or kidney technique, fails to disclose any evidence of cavitation, provided there is no apparent involvement on the opposite side, we do not feel that a secondary thoracoplasty is indicated in the attempt to obtain still more collapse. It is much more likely that active bronchial ulcerations containing tubercle bacilli exist and are the source of the tubercle bacilli in the sputum. Often bronchoscopy will reveal these ulcerations, but if not, it is more reasonable to assume that deep within the collapsed lung, at points not visible through the bronchoscope, ulceration does exist than to conclude that cavitation and parenchymal activity is still present. Many of the cases that are classified

as improved but not arrested, and have been held as unsuccessful, have positive sputum because of bronchial ulceration. The actively involved lung has been adequately collapsed and the cavities obliterated. A beneficial result has been procured.

Not the least disturbing complication following thoracoplasty has been pain. The scapula falls in against the transverse processes and proximal rib stumps, and either presses against intercostal nerves or puts tension upon them. In the attempt to relieve this pain, the patient raises his shoulder and scapula. Soon the scapula becomes adherent to the chest-wall; the arm can be raised little higher than the shoulder. The deformity often is marked. The pain is sometimes very distressing and for months or even years may prolong his incapacitation. While fatigue is usually due to toxaemia from the chronically infected collapsed lung, yet no small part of it often is due to continued pain from use of the upper extremity on the thoracoplasty side. During the past thirteen months we have resected short proximal sections of the intercostal nerves corresponding to the ribs removed. It is amazing how little postoperative pain the patient suffers. Often codeine is all that is required even for the first day. There is practically no scapular pain and the deformities have been much less frequent. Moreover, paralysis of the intercostal muscles, theoretically at least, further reduces the mobility of the collapsed lung.

In table 2 it is interesting to observe that, in clinics as widely separated as are these throughout the country, with three exceptions the percentage able to work approximated the average for the entire group. It is also noteworthy that of those patients who were dead at the end of the five year period, approximately 60 per cent died within the first eight weeks.

In a considerable percentage of the thoracoplasties done by Overholt in his series the apex was freed according to his modification of Semb's technique. It is quite surprising how little his results differ from those of a number of others where apicolysis was not included in the thoracoplastic collapse. In our own series we feel that, where a large apical cavity exists with its mesial wall close to the mediastinum, freeing the apex to the level of the fifth rib posteriorly appreciably increases the probability of complete cavity obliteration since in a cavity so located there is very likely to remain, following even an extensive thoracoplasty, a slit-like shadow in the X-ray film showing that cavity-walls are not actually in contact.

On the other hand, when the mesial walls of infraclavicular cavities

are situated some distance from the mediastinum, it seems to us better to allow the apex to remain hanging in its normal position. Complete removal, then, of the upper ribs during thoracoplasty we feel is more likely to result in complete cavity obliteration than by the procedure of apicolysis. We have found when cavities were so located that not infrequently with apicolysis they fell downward and inward toward the hilum and were so protected by the overlying lung in subsequent stages that complete obliteration was not obtained. The decision for resorting to apicolysis during thoracoplastic collapse should depend upon the relationship of the mesial wall of the cavities to the mediastinum.

TABLE 2

Summary of percentage of individual end results in 1,636 patients

	ABLE TO WORK	IMPROVED	UNIMPROVED	DEAD	
				8 Weeks	5 Years
Eloesser	36	12	9	5	14
Urquhart	43	32	11	9	4
E. C. Janes	30	9	31	17	12
Decker	17	24	34	12	12
R. M. Janes	28	37	17	6	4
Freedlander	46	19	13	7	7
Eggers	18	35	26	18	3
Raine and Yates	55	30	0	5	9
Gale	46	17	5	9	3
Thearle	41	40	13	4	2
Moore	24	55	7	7	7
Peters and Cornish	50	0	16	34	0
Overholt	41	14	3	7	7
Dolley-Jones-Paxton	40	14	7	10	9
Mean	38	25	15	11	7

The most startling figures in the survey are those shown in table 3. Our previous opinion, which was shared by many men in this group, was to the effect that a complete thoracoplasty was attended with a definitely higher death rate than a partial thoracoplasty and that a much smaller percentage of patients would be able to return to work; also, that there would be a considerably larger proportion permanently disabled. Yet the reverse in this series proved to be true. There were three times as many permanently incapacitated following partial thoracoplasty and the death rate following this procedure was one-third greater than when the thoracoplasty was complete.

It seems probable that the following factors are responsible for these apparently paradoxical figures:

1: The reluctance of both surgeon and patient to sacrifice more uninvolved lung than seemed absolutely necessary resulted in insufficient collapse of the lower portion of the involved lung. The removal of one or two more rib sections might have arrested the tuberculous process. If, however, these additional portions of ribs were excised, that particular patient would then have been changed from the category of partial thoracoplasty to complete.
2: An infection following the first or second stage not uncommonly precluded further stages so that at the completion of the thoracoplastic episode only partial thoracoplasty had been done, which in the end proved insufficient to produce a satisfactory result.

TABLE 3

Percentages of partial and complete thoracoplasty—before and after operations

	PARTIAL THORACOPLASTY	COMPLETE THORACOPLASTY
	per cent	*per cent*
Total cases 1,636	57	43
Before surgery:		
Permanently invalided	80	72
Able to do little work	8	9
Fibrotic process of the lung	50	45
After surgery:		
Permanently invalided	*14*	*5*
Able to do little work	24	26
Able to work	40	46
Dead 2 to 5 years	*20*	*14*

3: A tuberculous involvement of the contralateral side during the first two or three stages that would force a surgeon from further rib removals.

It seems reasonably safe to conclude, therefore, in spite of the figures given above, that if a partial thoracoplasty uneventfully and satisfactorily collapses that part of the lung involved by tuberculosis, the prognosis is better for rehabilitation and the mortality rate is lower than when the pulmonary tuberculosis is so extensive that complete thoracoplasty is necessary.

The summary of combined partial and complete thoracoplasties shows a striking contrast between the preoperative and postoperative condition.

Before thoracoplasty 91 per cent were reported as permanently disabled; following surgery 14 per cent. Before operation all were incapacitated. After surgical collapse 43 per cent were able to work. During the period of these statistics there were few clinics where thoracoplasty was advised except to those patients who had shown no beneficial response to any other method of treatment. Without thoracoplasty more than 90 per cent were held incurable, while following surgery but 14 per cent were totally incapacitated.

On the other hand, would not those patients who permitted thoracoplastic collapse have been about as well situated, perhaps, had they refused operation and utilized the time consumed in recovery following

TABLE 4

Freedlander's comparative results

85 patients who accepted thoracoplasty
58 patients who refused thoracoplasty

	per cent
With thoracoplasty—Cavities closed, sputum negative	57
Without thoracoplasty—Cavities closed, sputum negative	10
With thoracoplasty—Improved	9
Without thoracoplasty—Improved	7
With thoracoplasty—Unchanged or worse	13
Without thoracoplasty—Unchanged or worse	49
With thoracoplasty—Dead	14
Without thoracoplasty—Dead	26

surgery to continuing their cure with or without less radical procedures? Table 4 prepared from Freedlander's comparative results seems to answer satisfactorily this question. There was approximately the same number of patients among those who had thoracoplasty and those who elected to continue without it. When the end results were compared there were nearly twice as many dead among those who had refused thoracoplasty than those who had accepted it. Nearly six times as many had negative sputum and apparent cavity closure among those who had thoracoplastic collapse than among those who saw fit to continue their cure without it. In Freedlander's entire series (good chronics and slipping chronics combined) thoracoplasty increased by four times the chance of

operative improvement and decreased by two-thirds the possibility of becoming worse.

Certain obviously important conclusions can be drawn from the combined results of the work studied in this analysis which will no doubt appreciably increase the rehabilitation rate and will markedly decrease the death rate following thoracoplasty. Avoidable disasters that have occurred in the past will be lessened. The possibility that the anterior cavity wall may require the removal of costal cartilages for complete closure will regularly be given consideration. A considerable percentage will be additionally benefited by apicolysis.

The results two to five years following thoracoplasty of this very considerable series of cases taken from fourteen well known clinics throughout the United States, in conjunction with the controlled series of Freedlander's, are sufficiently conclusive to warrant the conviction that people, afflicted with far advanced pulmonary tuberculosis and apparently permanently incapacitated by their disease, have a much better prospect for arrest of their tuberculosis if they accept thoracoplasty than if they refuse it.

In a comparison of the figures in this article there seem to be many discrepancies. Actually this is not true. The various contributors were unable to answer accurately certain questions in regard to a variable number of their patients who had undergone thoracoplasty. We had to summarize for every particular statement, therefore, only the actual number of those patients of whom they had a definite knowledge on each separate point that was under consideratian.

INTRAPLEURAL PNEUMONOLYSIS BY THE CLOSED METHOD[1, 2]

Impressions after Fifteen Years' Experience with 350 Cases

RALPH C. MATSON

The problem of the open tuberculous cavity is constantly attracting more attention on the part of those engaged in the medical and surgical treatment of pulmonary tuberculosis—and rightly so, because the carrier menace of the ambulant patient with cavity is too grave to disregard; besides, an open cavity case, though not ambulant, is a constant source of infection to the opposite lung, larynx and gastrointestinal tract—too often rendering the case incurable.

The value of artificial pneumothorax in closing open cavities is admitted by every phthisiotherapeutist. But its application has been very much abused. I have often stated that the greatest indictment against those utilizing pneumothorax therapy is the persistence with which it is continued for months, and often for years, when a survey of the clinical, roentgenological and laboratory data should make it obvious that the pneumothorax is useless because of adhesions preventing closure of a cavity or preventing adequate rest of the lung.

The following case is a typical example of many I could cite where a prolonged useless pneumothorax deprived the patient of the benefits of surgical collapse.

While attending a medical meeting some years ago, I was one of a half dozen guests invited to discuss the surgical treatment of pulmonary tuberculosis. The subject assigned to me then was the same as that I shall discuss to-day. Another guest was an experienced thoracic surgeon whose knowledge of severing adhesions in artificial pneumothorax had never advanced beyond what he had read about the original Jacobaeus instruments and technique. He had no background of pneumothorax work. We were both called in consultation by a well known

[1] Presented at the 33rd annual meeting of the American Sanatorium Association, Los Angeles, California, June 20, 1938.

[2] From the Department of Surgery, University of Oregon Medical School, Portland, Oregon, and the Portland Open Air Sanatorium, Milwaukee, Oregon.

phthisiotherapeutist whose experience in collapse therapy, at the time, was limited to a brief pneumothorax career with no knowledge whatsoever of the technique of severing adhesions. The case history is, briefly:

Female, age 24 years, had been ill three years. During the first year she carried out a rest cure in a sanatorium, with no improvement. A study of her X-ray films and records revealed that the small cavity in the left upper lobe, which she had originally, had become progressively larger; she had lost in weight, her sputum quantity increasing. Upon arrival at the second institution, a pneumothorax was instituted; a marked improvement resulted during the first three months; her temperature became more stabilized, loss of weight was arrested and the sputum quantity reduced. After the third month she continued to raise the same quantity of sputum in twenty-four hours and her condition remained more or less stationary for six months before the consultation referred to above, when her condition swerved retrogressively. She had lost in weight and strength, and began carrying an afternoon temperature with an increased sputum quantity.

Study of her X-ray film at that time showed that she had a very inadequate pneumothorax. A band adhesion was seen holding open a large cavity. There was fluid in her pleural cavity and distinct evidence of a beginning spread to the opposite lung. I recommended a thoracoscopic examination and severing the adhesion if possible,—otherwise, abandonment of the pneumothorax, and consideration of other surgical collapse procedures. My colleague advised continuation of the pneumothorax, believing that in this way the adhesion would stretch sufficiently without other measures. The doctor who called us in consultation also agreed with my colleague. Six months later she was sent to me from a distant point to have the adhesion severed. However, it was not necessary to introduce the thoracoscope to see that the operation would be utterly useless. A roentgen film showed that she had widespread metastatic disease in her opposite lung, with distinct cavity formation. Added to this, tuberculosis of the larynx was interfering with nutrition, and her gastrointestinal tract was uncontrollably invaded with the disease. Her general condition was bad; she was running a high temperature and a diagnostic puncture revealed an empyema. She was returned to her home and two months later she died.

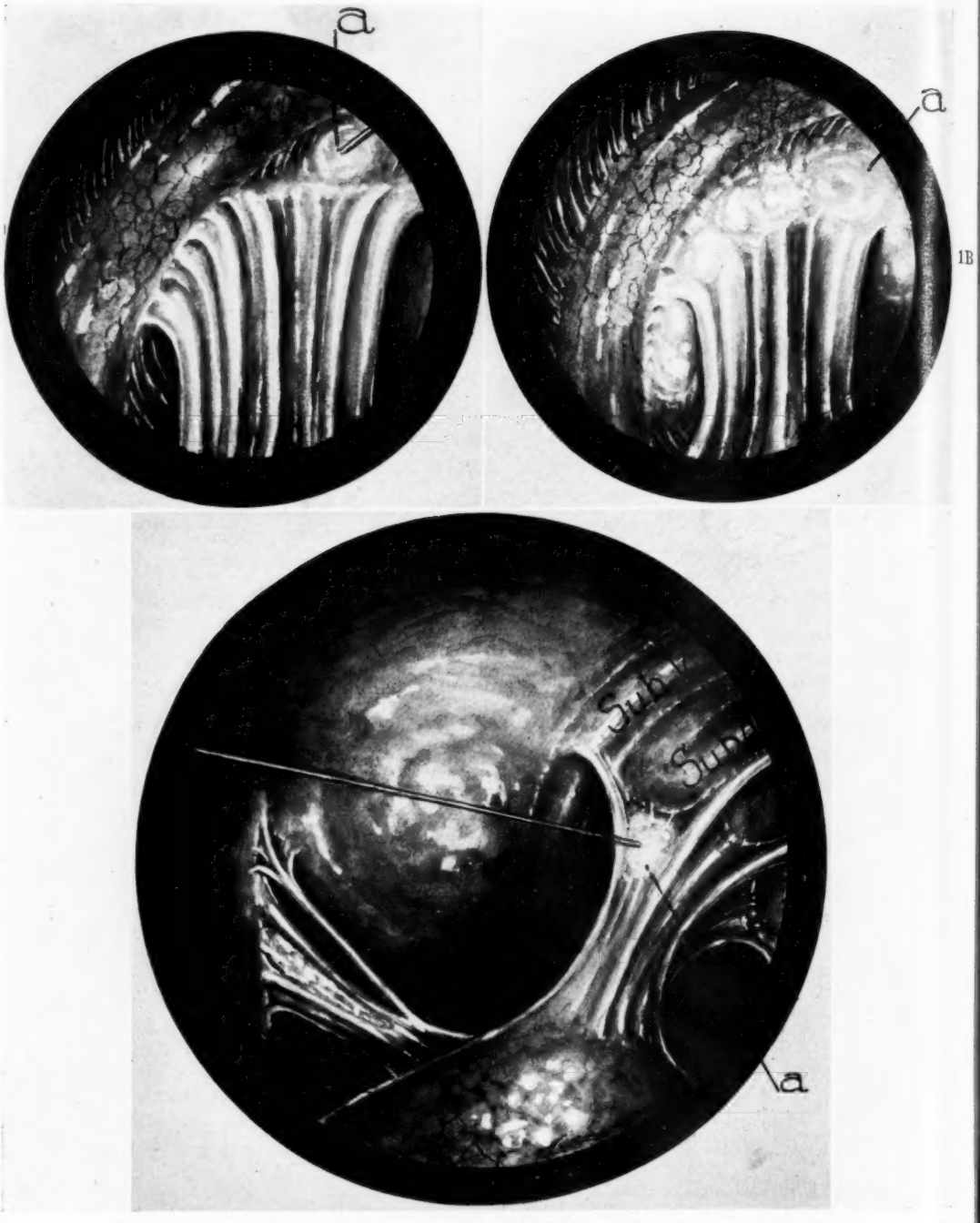
Many still sanction a lengthy trial of an unsatisfactory pneumothorax, hoping eventually to stretch offending adhesions, thereby providing a satisfactory pneumothorax. We advocated this method as late as 1922, after obtaining disappointing results with the original Jacobaeus instruments and technique. With the development of the Unverricht thoracoscope, we again resorted to the Jacobaeus technique, nevertheless

utilizing the Unverricht thoracoscope, which gave a much better field of vision. The results were an improvement over attempts to stretch adhesions, but left much to be desired because of complications naturally associated with the intrathoracic use of the actual cautery. Electrosurgery was then rather extensively used in cancer surgery and it seemed reasonable that it could also be applied intrathoracically with the development of a fitting technique and proper instruments. The first high-frequency unit on the market proved unsatisfactory. But when the Bovie unit was introduced, it seemed suitable for this special type of surgery, whereupon it was adopted and instruments and technique developed which I am convinced surpass the galvanocautery. As for the open method that many thoracic surgeons cling to, I still maintain that any adhesions operable by the open one can be severed more readily by the closed method with much less danger to the patient. A well known thoracic surgeon stated recently that adhesions are blindly cut under thoracoscopic vision, with no possibility to ligate blood vessels. I challenge both statements, and advise greater study on the part of those opposed to the closed method.

I am constantly being asked to express an opinion regarding the relative merits of various operating thoracoscopes, utilizing a single puncture, as compared with the technique which I employ—introducing the thoracoscope at one point and the operating electrode at another. My reply is that I have been requested by manufacturers to test various operating thoracoscopes, none of which I can sincerely recommend after a trial. Having operated on a large number of cases where numerous adhesions were located throughout the pneumothorax cavity, my experience convinces me that these could not have been severed with an operating thoracoscope without making a second puncture to afford an additional approach. In the method I employ, one introduces the thoracoscope (an Unverricht or Julian Moore model) at a point selected after study of the stereoscopic films; a careful survey is made of the pneumothorax cavity, noting the number, character and distribution of adhesions. A point is then decided on to introduce the operating electrode, one which will permit a satisfactory approach to all adhesions. In case of many large band and curtain adhesions situated in the pleural cupola or the posterior upper quadrant of the pneumothrax cavity, it is often desirable to study adhesions from two points of view. This can always be done by the two-puncture method, as the cannulas are the same size for the thoracoscope and operating electrodes and permit interchange of instruments.

The relative merits of the galvanocautery and high-frequency current will be discussed later in the subject of complications. But here I wish to dwell upon another matter, namely, that of painful muscle reflexes caused by the high-frequency current. This one objectionable feature is considerably stressed in the literature, inasmuch as, due to it, the operation is often rendered impossible. Some years ago I, myself, was compelled to discontinue the operation on a case because of painful muscle spasm. But subsequently I found I could infiltrate the endothoracic fascia at the base of the adhesion with one per cent novocaine-suprarenin solution and so force the parietal pleura (to which the adhesion was attached) away from the chest-wall, and sever the adhesion at its base painlessly and without bleeding, leaving its stump covered with parietal pleura. This local anaesthesia infiltration was made under thoracoscopic guidance, the needle being passed through the chest-wall at the base of the adhesion down through the parietal pleura to the endothoracic fascia. However, many extensive adhesions are often encountered where one side only could be anaesthetized in this manner. To surmount that disadvantage, I had some fourteen-inch 21-gauge needles constructed, and now my usual procedure is to pass these needles through the cannula for the operating electrode, and under thoracoscopic guidance carry out the whole infiltration anaesthesia intrathoracically (figure 1). By this means the problem of painful muscle reflexes is entirely overcome. In addition, certain types of adhesions, where prolongations of cavities are often found extending up to the chest-wall, may be safely severed by forcing the parietal pleura, at its base, away from the chest-wall by infiltrating the endothoracic fascia and severing around the base through the parietal pleura. As the incision is completed, the stump of the adhesion falls away from the chest-wall covering with the parietal pleura, which prevents the stump from opening and forming a spontaneous pneumothorax. Tent adhesions are a good example of a type that this method will cope with satisfactorily.

The same intrathoracic method of infiltration lends itself to solving another problem—that of dealing with adhesions attached to important blood vessels, particularly the subclavian artery or vein. Some of these adhesions are bands and, though fairly short, are operable. A few years ago I would have hesitated severing such adhesions, lest the current pass to the wall of the vessel and cause damage. And using the galvanocautery for these types of adhesions, as every conservative surgeon knows, would be unthinkable because of secondary tissue necrosis. Utilizing the long needles (previously described) under thoracoscopic guidance,



1A 1B

2

FIG. 1. A: A 21-gauge fourteen-inch needle is introduced through the cannula for the operating electrode. The tip of the needle (a) rests in the endothoracic fascia and shows beginning infiltration, with novocaine-suprarenin solution, of the chest-wall attachment of a band adhesion. B: Completed infiltration of the base of the adhesion (a) shown in A.

FIG. 2. Point of 21-gauge fourteen-inch needle introduced into band adhesion 1 cm. from subclavian vessels (a), showing beginning infiltration with novocaine-suprarenin solution under thoracoscopic guidance.

one can inject the novocaine-suprarenin solution thoroughly into an area the size of which depends on the type of adhesion and the point at which it is to be cut (figure 2). The following case may illustrate the technique:

Numerous band adhesions which held open an apical cavity had been severed, but there still remained one short band, 2 cm. wide and between 3 and 4 cm. long; this was attached to the subclavian artery and vein. Under thoracoscopic vision, an area 2 cm. wide was well infiltrated in the adhesion adjacent to the vessel (figure 2a) and the adhesion severed with a moderately damped current at a point 2.5 cm. from the vessel. The current was seen to pass up to the point of the infiltration, but not beyond it. The cutting was clean and the field dry. Had the infiltration not been used, the coagulation would have passed to the wall of the vessel and possibly damage might have resulted.

I have employed this technique repeatedly and commend it highly.

Now, as to the relative results of the galvanocautery and high-frequency current, the cauterization of adhesions with the galvanocautery is objectionable because of heat, smoke and reaction to operation. Perhaps its greatest shortcoming is the character of the cutting as tissue is destroyed oftentimes only a short distance from the cut. Thus, blood vessels are often severed without any previous obliteration. Unless a dull red heat is used (dark room control), undue bleeding may take place; in addition to this danger, if too much heat is employed, there is also the possibility of tissue necrosis occurring, which may involve the parenchyma of the lung, tuberculous cavities or tuberculous foci, resulting in spontaneous pneumothorax and empyema.

TABLE 1

Comparative frequency of exudate formation following various operative methods—350 cases

	JACOBAEUS METHOD	AUTHOR'S METHOD	
	Galvanocautery, 136 cases	Unnamed high-frequency units, 35 cases	Bovie high-frequency unit, 179 cases
	per cent	*per cent*	*per cent*
Serous exudate	20.5	31.4	3.9
Purulent exudate	26.4	11.4	2.8
Haemorrhagic exudate	10.3	31.4	1.6

The advantages of the high-frequency current are illustrated in the following material: (table 1) 136 cases were operated upon by the gal-

vanocautery technique of Jacobaeus. Next, a small group of 35 cases were operated upon by the electrosurgical method, utilizing the first type of high-frequency machine to appear on the market. It will be noted that both haemorrhagic and serous exudate formation was very much increased in frequency, but empyema formation was reduced to less than one-half. Then, with improved instruments, added experience and better technique, 179 cases were operated upon by my method, utilizing the Bovie unit. This resulted in an enormous reduction of exudate formation (serous exudate 3.9 per cent, purulent exudate 2.8 per cent, haemorrhagic exudate 1.6 per cent). The source of blood in the few cases of haemorrhagic exudate was not from bleeding of severed adhesions, but from the first chest-wall puncture for introducing the thoracoscope, where a small quantity of blood ran down the inner chest-wall as the trocar and cannula for the thoracoscope passed through the pleura. Severe febrile reactions are now rare. Bronchopleural fistula has occurred six times, 3.8 per cent; spontaneous pneumothorax three times, 1.6 per cent; there were no instances of shock, gas embolism nor severe surgical emphysema. Likewise, no direct operative mortality exists in the entire series: only one death occurred for which the operation was possibly indirectly responsible, and this single mortality was due to a spontaneous pneumothorax on the contralateral side during a severe asthmatic paroxysm seven days after operation. Excepting three profuse haemorrhages early in our work, we have had no serious sequelae. Records of the results of treatment in a series of 350 cases show 70 per cent have been clinically successful, that is, the unsatisfactory pneumothorax was converted into a satisfactory one and all the patients returned to working capacity with a negative sputum; whereas, before operation 90 per cent had a positive sputum and 85 per cent were bed cases.

CONCLUSION

Intrapleural pneumonolysis, when utilized to the extent it merits, will preclude the necessity of innumerable major operations on cases wherein the former is appropriate. Convinced by experience, I am certain that a three to five months' trial will determine the efficiency of an established pneumothorax. It is a mistake to subject the patient to a prolonged trial of pneumothorax therapy, hoping to stretch adhesions and provide a satisfactory pneumothorax, thus frequently denying the patient the benefit of other surgical procedures because the disease has become too extensive for any means of intervention.

ASYNCHRONY OF THE MOVEMENT OF THE LOWER RIBS FOLLOWING PARALYSIS OF THE HEMIDIAPHRAGM

A Test for Diaphragmatic Paralysis after Operations on the Phrenic Nerve

JEROME R. HEAD[1]

Since the time of Galen the influence of diaphragmatic contraction upon the movement of the lower ribs has been actively disputed. Galen, who was the first to recognize that respiration was a muscular act, believed that its contraction raised them gently upwards—*suaviter in sursum*. Von Haller disagreed with Galen, holding that the force of the diaphragm was applied in a transverse medial direction and consequently that it opposed and limited costal excursion. Hoover, who devoted considerable study to the matter, concluded that conditions tending to raise the dome of the diaphragm, such as subdiaphragmatic accumulations of fluid, made it function according to the Galenic theory, while conditions tending to depress it or to obliterate the costophrenic angle, such as emphysema, fluid in the pleural cavity or adhesions, made it pull the ribs inward. From these observations he described what has since come to be called the "Hoover sign," an increased excursion of the lower ribs on the affected side in the presence of subdiaphragmatic effusions.

In 1930 I (1) reviewed the literature on this subject and reported the results of experiments performed upon dogs. From these and from clinical observations it was concluded that under normal conditions the diaphragm was an antagonist of the intercostal muscles, both by direct muscular action on the ribs to which it is attached and indirectly on the other ribs by decreasing the pressure in the pleural cavity. It was believed then that paralysis of one-half of the diaphragm permitted an increase in the movement of the ribs on the homolateral side. It was also stated that theoretically the diaphragm might raise the ribs during the first part of its descent and limit their motion as it flattened and its pull became more transverse.

Close pre- and postoperative observation of patients submitted to

[1] Chicago, Illinois.

phrenicectomy has convinced me that the conclusions reached from the reported experiments are only partially correct and that what from theory was surmised might take place does actually occur. In the experiments graphic records were made of the movements of the lower ribs before and after section of one phrenic nerve. The total movement was measured during a complete respiratory cycle without analysis of the rate of movement during the early and late phases of inspiration. Since then it has become apparent that the most obvious alteration in costal movement is an asynchrony, the ribs on the affected side lagging behind the opposite ones during the first part of a deep inspiration, but then, as the opposite

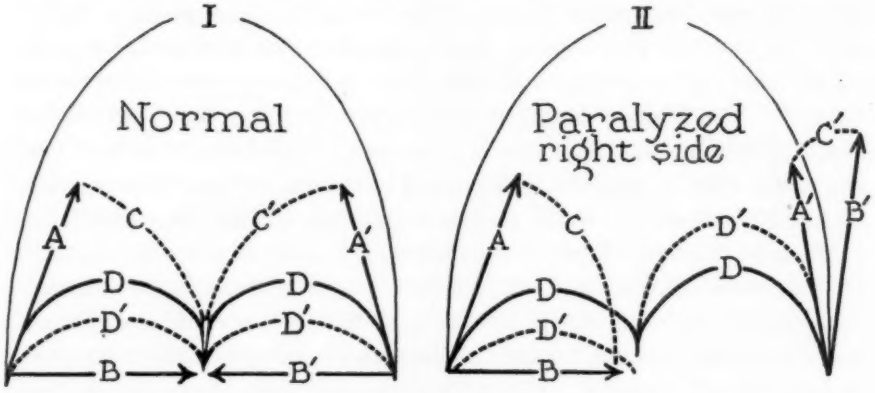


DIAGRAM I. The diaphragm, D–D, in the inspiratory position. A and A′, the lines of force, at the beginning of contraction change along the arcs C and C′ until eventually they lie in the line of B–B′.

DIAGRAM II. The diaphragm, D–D, in the inspiratory position when one-half is paralyzed. In the first phase the paralyzed side moves down and the sound side moves up. During the second phase the paralyzed side exerts some lifting action (line B′) along the arc C′ on the ribs to which it is attached.

ones become opposed by the flattening diaphragm and their movement restricted, overtaking and passing them during the second half of deep inspiration.

The mechanism of this asynchronous movement can best be explained by reference to the accompanying diagrams. As the highly arched diaphragm (D–D, diagram I) begins to descend from its expiratory position it exerts a pull upon its costal attachments in the direction of the lines A and A′. As it descends these lines of force change direction along the arcs C and C′ until, when the diaphragm becomes flat, they are in the direction of lines B and B′. Thus during the first

part of inspiration the contracting diaphragm tends to raise the ribs to which it is attached. During the latter part it tends to draw them inward and downward.

If one-half of the diaphragm is paralyzed (see diagram II) its lifting action is absent during the first phase of inspiration while on the sound side it is still present. Consequently as inspiration begins the ribs on the sound side move more rapidly. As the functioning diaphragm continues to descend it eventually stops the movement of the ribs to which it is attached while the paralyzed diaphragm, moving now in a paradoxical direction, under the influence of the increasing intraäbdominal pressure and the decreasing intrapleural pressure, exerts some lifting action (line B′) on the ribs to which it is attached. During the latter part of inspiration the ribs on the affected side move more rapidly than those on the sound side.

There are two other factors which contribute to this late exaggeration of movement. The fact that the diaphragm is not helping to expand the lung, is, in fact, rising into the pleural cavity, makes it easier for the ribs to expand the lung and so permits them to move more rapidly. At the same time the descending diaphragm on the opposite side forces the abdominal viscera out of the corresponding hypochondrium and into that on the side on which the diaphragm is paralyzed. This shifting of the abdominal viscera acts not only to raise the paralyzed diaphragm but also to force outward the lower ribs.

CONCLUSIONS

1. Under normal conditions, during the first phase of deep inspiration contraction of the diaphragm helps to elevate the ribs to which it is attached. As inspiration proceeds and the diaphragm becomes flattened, it exerts a pull in a medial direction and thus opposes the muscles acting to raise the ribs.

2. When one-half of the diaphragm is paralyzed the movement of the lower ribs on the two sides becomes asynchronous. During the first phase of inspiration those on the sound side move more rapidly; during the later phase the movement of those on the opposite side is accelerated.

3. Recognition of this phenomenon provides a clinical test of the effectiveness of operations on the phrenic nerve.

REFERENCE

(1) HEAD, J. R.: The redistribution of respiration following paralysis of the hemidiaphragm, Surg., Gynec. & Obst., 1930, *50*, 929.

CHLORINE FOR THE INDUCTION OF ARTIFICIAL PNEUMOTHORAX[1]

A Preliminary Report

K. S. RAY, N. N. SEN AND H. N. DASGUPTA

From a review of the literature regarding the use of different gases for the production of artificial pneumothorax, it appears that the main considerations for selecting different gases have been twofold: (*a*) to find one that is least absorbed from the pleural cavity so as to obviate the necessity of frequent refills (nitrogen and helium have been used for this purpose); (*b*) to use a gas which will be most readily absorbed by the blood and prove harmless should embolism accidentally occur (oxygen and carbon dioxide have been used with this object in view). Further investigations by Rist and Strohl (1), confirming the previous observations of Webb, Gilbert, James and Haven (2), have shown that there is no advantage in using anything but ordinary atmospheric air.

Analysis of gas withdrawn from pleural cavity in artificial pneumothorax has shown that no matter what gas is introduced diffusion takes place and after a time the composition is approximately:

Oxygen	1 to 2 per cent
Carbon dioxide	7 to 8 per cent
Nitrogen	90 per cent

With improvement of technique, gas embolism hardly ever occurs nowadays and ordinary atmospheric air, which is as good as any gas, is therefore extensively used.

It will be noticed that, in selection of a gas, attention was paid mainly to mechanical factors of compression. Obliteration of cavities, removal of toxaemia, lymph stasis which promotes fibrosis and other salutary effects of pneumothorax therapy are dependent on the mechanical factor and are therefore common to all gases. But no work appears to have been done with a view to introducing an antiseptic element. The value of chlorine as a disinfectant is well known and it occurred to us that we might in a series of cases combine the pressure effects with the germicidal

[1] From the Jadabpur Tuberculosis Hospital, Calcutta, India.

properties of chlorine; we thought it safer to start with a low dilution of one per cent.

Chlorine was prepared by heating manganese dioxide and hydrochloric acid, and starch iodide solution was employed for its detection.

Dilution of chlorine for use in pneumothorax proved to be a difficult problem but we were able to solve it in a very simple way. We did this in our pneumothorax apparatus (Lilingston and Pearson type) by collecting chlorine in the graduated bottle by displacement of water and then diluting it to the required strength by drawing in air. The only objection against it is rapid solubility of chlorine in water. This undoubtedly did occur during the initial stages but by collecting chlorine repeatedly over the same water it became saturated with chlorine and the margin of error was reduced to a minimum. Before introduction, air was expelled from the tubing and the gas from the apparatus tested for chlorine. We must confess that we have not done any experimental work to establish the bacteriostatic power of diluted chlorine either *in vitro* or *in vivo*. The scope of the present paper is confined to the study of clinical results.

The use of chlorine was started in November, 1933 and had been attempted in 102 cases discharged till the end of August, 1936. Out of these, 28 cases have been excluded either because pneumothorax could not be induced, or because pneumothorax was abandoned after a few tentative refills. The total number of cases considered in this review is 74.

For the purpose of comparison, 71 cases treated with pneumothorax with air, from the middle of 1931 to the end of August, 1936, have been included.

It was apprehended that irritant properties of chlorine will stand in the way of its general use. Before considering the results of treatment, therefore, we propose to take up this question. Comparative tables of pleural complications are given below. Other complications not being peculiar to chlorine have not been included.

Pleural complications

	NUMBER OF CASES	OBLITERATIVE PLEURITIS	PLEURITIS WITH EFFUSION	TOTAL
Pneumothorax with chlorine 1 per cent.....	74	21 (28.4%)	8 (10.8%)	29 (39.2%)
Pneumothorax with air.....	71	11 (15.5%)	11 (15.5%)	22 (31.0%)

It will be noticed that the percentage of complications is higher in the chlorine group, 39.2 per cent as against 31.0 per cent in the air group. There are two factors which stand out prominently: (*a*) Chlorine does not cause massive effusions any more than ordinary air. (*b*) Irritant action of chlorine is confined to production of obliterative pleuritis. This occurred in 13 per cent more cases in the chlorine group.

Let us now proceed to consider the result of treatment of these groups.

Results of treatment

	NUMBER OF CASES	GOOD RESULTS		NO IMPROVEMENT
		Arrested	Quiescent or much improved	
Pneumothorax with chlorine 1 per cent.....	74	36 (48.7%)	24 (32.2%)	14 (18.8%)
Pneumothorax with air.....	71	23 (32.4%)	32 (45.0%)	16 (22.6%)

From a comparison of the foregoing tables, it will be seen that although the total good results for both groups did not show much difference, the percentage of cases arrested was greater with chlorine.

Further analysis of the data brings out the interesting fact that the salutary effects of chlorine were more marked in cases where the lungs could only be partially collapsed by pneumothorax. The following table illustrates the point.

	PERCENTAGE OF GOOD RESULTS		PERCENTAGE OF ARRESTED CASES	
	Chlorine	Air	Chlorine	Air
Collapse satisfactory.....	39.2	42.0	27.0	22.6
Collapse unsatisfactory.....	36.6	40.8	21.7	9.8

Let us now proceed to examine as to how far these beneficial results can be attributed to the introduction of chlorine. There are two factors which make any direct effect of chlorine highly improbable: (*a*) 52.1 per cent of chlorine cases received as an adjunct to pneumothorax therapy 2.5 grams of some gold preparation (sanocrysin or solganol). Only 37.8 per cent of air cases were treated with this amount of gold. (*b*) The germicidal effect of chlorine should show itself in the higher

percentage of negative sputum in the treated cases. The actual results did not show much difference as the following table will show.

	NUMBER OF CASES	ADMITTED WITH POSITIVE SPUTUM	SPUTUM RENDERED NEGATIVE
Pneumothorax with chlorine	74	60 (81.0%)	33 (55.0%)
Pneumothorax with air	71	61 (86.0%)	37 (60.7%)

Chlorine had no appreciable effect on fever or haemoptysis, nor did it influence the course of extrapulmonary lesions in any way.

SUMMARY AND CONCLUSIONS

1. A résumé of the comparative clinical results of 74 cases of pneumothorax with 1 per cent chlorine and 71 cases of pneumothorax with air is given.

2. Judging by the percentage of negative sputum in the treated cases, chlorine did not exert any germicidal effect.

3. Our object in publishing this paper is to stimulate discussion and research in regard to the use of an antiseptic element in pneumothorax to enhance its therapeutic value.

We are thankful to our colleagues of the Jadabpur Tuberculosis Hospital for collaboration and assistance and to Dr. R. B. Lal, Director of All-India Institute of Hygiene, Calcutta, for permission to use the statistical machines of the Institute.

REFERENCES

(1) Rist, E., and Strohl, A.: Ann. de méd., 1920, *8*, 233.
(2) Webb, Gilbert, James and Haven: Arch. Int. Med., 1914, *14*, 883.

PRECORDIAL FRICTION RUB IN SPONTANEOUS PNEUMOTHORAX

MILTON R. LOURIA[1]

The development of a loud precordial friction rub shortly after the occurrence of spontaneous pneumothorax is an interesting phenomenon which apparently has not previously been reported in the literature. Spontaneous pneumothorax complicating artificial pneumothorax occurs not infrequently. Following the discovery of the first case in which a precordial friction rub developed shortly after the spontaneous pneumothorax occurred, all subsequent cases of spontaneous pneumothorax were carefully examined for the appearance of this sign. However, in a fairly large series of cases of spontaneous pneumothorax, such as one encounters on an active tuberculosis service, only one other instance of this same condition was noted during a period of several years. The friction rub is of interest from the point of view of the causative mechanism and also of the interpretation of its clinical significance.

Case 1: E. M., a white female, age 27, single, was admitted to the Kings County Hospital (service of Dr. Charles E. Hamilton) on November 1, 1935. The patient gave a two-month history of cough, weakness, loss of weight and pain in the left chest which was exaggerated on deep breathing or coughing. Physical examination and X-ray showed evidence of an extensive caseous pneumonic lesion in the left upper lobe. The sputum was positive for tubercle bacilli.

On November 16, initial pneumothorax was given on the left side with satisfactory negative readings. No difficulty was noted in the induction of pneumothorax. Treatments were given at the usual intervals and satisfactory collapse of the left lung was maintained. On February 19, 1936, three months after the beginning of pneumothorax, the patient experienced sudden pain in the left chest accompanied by severe dyspnoea. Examination showed marked displacement of the heart to the right side. Breath-sounds were absent over the left side of the chest. Except for tachycardia, no abnormality of the heart sounds was noted. A diagnosis of left spontaneous pneumothorax was made. Manometric readings were +10, +22. A deflation (1,500 cc.)

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was carried out with complete relief of the patient's respiratory distress. Final manometric readings were −6, 0. During the next few weeks, frequent X-ray examinations were made. It was apparent that the bronchopleural fistula was closed as the lung expanded rapidly. Three weeks after the first spontaneous pneumothorax, manometric readings were −12, −6. Three hundred cc. of air were given with final readings of −8, −3. Nine days later the patient again experienced sudden pain in the left chest and severe dyspnoea; the physical signs again were those of spontaneous pneumothorax. A deflation (2,500 cc.) was carried out immediately with relief of the respiratory embarrassment. On the following day, the patient was found to be quite comfortable. Examination showed the heart displaced very slightly to the right. The cardiac rhythm was regular; the sounds were of good quality. No murmurs were heard but there was a faint friction rub, synchronous with the cardiac cycle, and heard only over the region of the cardiac apex. On the following day, the patient's clinical condition was satisfactory. Further deflation was not necessary. Examination now disclosed a very loud, harsh friction rub which was heard over the entire precordium but was of maximum intensity in the fourth left interspace in the midclavicular line. This sound had the harsh grating quality which one is accustomed to associate with a pleural friction rub. In contrast, however, to a pleural friction murmur, the sound was best heard when the patient held her breath. The friction rub was entirely synchronous with the cardiac cycle; it was louder in the systolic than the diastolic phase. On rotating the patient, the intensity of this abnormal sound was definitely diminished; this was noted particularly with rotation to the left. Furthermore, this manoeuvre enabled the examiner to dissociate the friction murmur from the heart sounds. As one rotated the patient slowly, the friction rub gradually diminished in intensity and simultaneously the heart sounds, quite normal in character, could be heard with greater clarity. With the patient lying on her left side, the friction murmur became very faint while the cardiac tones retained their usual quality. It thus seemed quite definite that any endocardial component could be ruled out. The friction rub was relatively uninfluenced during respiration; on the left side breath-sounds were very faint due to the almost complete collapse of the lung. However, the exaggerated breath-sounds of the right lung were transmitted so that in usual or in forced respiration the friction rub was heard together with a respiratory murmur. Because of the recent spontaneous pneumothorax, no attempt was made to examine the patient in the sitting position. Examination five hours later showed a moderate decrease in the intensity of the friction sound with no alteration in the character of the heart sounds. The friction rub disappeared completely in two days. There was no evidence, on X-ray or physical examination, either at this time or subsequently, of development of fluid in the pericardial sac. In view of the re-

current spontaneous pneumothorax, it was decided to abandon pneumothorax therapy and perform a thoracoplasty. The lung expanded without difficulty. During the stage of expansion, the friction rub did not reappear.

Case 2: H. W., a white male, age 32, was admitted to the Kings County Hospital on November 9, 1935, with the complaint of tightness in the chest and difficulty in breathing of two days' duration. The patient was a known case of pulmonary tuberculosis receiving artificial pneumothorax on the right since October 12, 1932. His last refill was given two weeks before admission. At this time 200 cc. were given with final readings of +10, +12. There was no immediate reaction. The symptoms of respiratory difficulty appeared twelve days later.

On admission, the patient was markedly dyspnoeic. The physical findings of importance were limited to the thorax. Respiratory excursion of the right side of the chest was diminished. Percussion note was hyperresonant on the right with absent breath-sounds on this side. The left lung revealed no abnormalities except exaggerated breath-sounds. The heart and mediastinum were somewhat displaced to the left. The cardiac rhythm was regular, rate 110. The cardiac sounds were of good quality; no murmurs or other adventitious sounds were heard.

The diagnosis on admission was right spontaneous pneumothorax, superimposed on an artificial pneumothorax. Manometric readings on the right showed intrapleural pressures of +18, +24. A deflation (550 cc.) was done with considerable relief of the dyspnoea. The patient remained quite comfortable and further deflation was not found to be necessary. An X-ray film taken six days after admission showed a pneumothorax on the right side with practically complete collapse of the lung and a minimal effusion in the costophrenic angle.

Nine days after admission, routine examination disclosed a loud precordial friction rub of maximum intensity along the left sternal margin. The friction rub was synchronous with the cardiac cycle and was louder in the systolic phase. As in the previous case, it was heard most clearly when the patient held his breath. The intensity of the murmur was diminished by rotation of the patient to either side. By this manoeuvre, it was again possible to dissociate the friction murmur from the normal heart sounds. It is noteworthy that the patient had no new complaints at this time. There was no increase in the cardiac rate; the heart sounds were of good quality; there was no precordial pain.

During the next few days there was a rapid accumulation of fluid in the right pleural cavity. Simultaneously the friction rub became progressively fainter and disappeared completely in three days. At no time was there clinical or X-ray evidence of a pericardial effusion.

The patient subsequently developed a mixed tuberculous empyema on the right side. Drainage and thoracoplasty were carried out; the patient recovered.

COMMENT

The first question that arises concerns the possibility of this precordial friction sound being due to pericarditis. As is well known, acute serofibrinous pericarditis occurs most commonly in association with rheumatic fever, pneumonia, sepsis and nephritis. Obviously, none of these conditions existed in the reported cases. Tuberculous pericarditis must also be considered but it would seem more than unlikely to have this lesion appear exactly at the time of the onset of the spontaneous pneumothorax. Furthermore, the short duration of the friction rub, not accompanied or followed by any alteration in the quality or the intensity of the heart sounds, speaks against pericarditis being the causative factor. In neither of the reported cases was there evidence of subsequent accumulation of fluid in the pericardial sac.

Hamman (1) has described an unusual crunching, bubbling sound heard over the precordium and of maximum intensity near the apex, which apparently resulted from an interstitial emphysema of the lungs. In several cases the sound was brought out only when the patient was lying on the left side. This sound, as described by Hamman, had none of the characteristics of the friction murmur heard in the author's cases. However, the cases reported by Hamman furnish another striking example of unusual sounds which may be heard over the precordium but do not signify the presence of any cardiac or pericardial pathology.

The more likely explanation of the friction murmur is that it was of pleuropericardial origin. According to Norris and Landis (2) a pleuropericardial friction murmur "occurs as a rule along the left border of the heart, and is caused by a roughened inflamed spot on the pleura coming in contact with a similar area on the external surface of the pericardium." It seems hardly necessary to postulate the existence of two inflamed areas; the presence of an inflamed or a fibrinous area on either the pleura or the external surface of the pericardium would seem mechanically sufficient to give the acoustic effect of a friction murmur. Both of the reported cases had had a previous artificial pneumothorax because of caseous pneumonic tuberculosis. It is well recognized that the pleura in such cases is the seat of fibrinous changes. Apparently, with the onset of the spontaneous pneumothorax, a lappet of lung with a roughened

pleural surface was brought in contact with the external pericardial surface. The disappearance of the friction murmur after a few days may be accounted for by beginning expansion of the lung or by the formation of a small amount of fluid.

In regard to the clinical significance of this friction murmur, little need be said. In the reported cases it was of short duration and was not accompanied by other clinical manifestations such as precordial pain or alteration in the cardiac status. Unfortunately, no electrocardiographic studies were done during the time that this murmur was audible. The friction sound would seem to be of importance only from the point of view of not interpreting the sign as evidence of a true pericarditis.

SUMMARY AND CONCLUSIONS

1. Two cases are reported in which a loud precordial friction murmur was heard shortly after the occurrence of a spontaneous pneumothorax superimposed on an artificial pneumothorax.

2. This friction murmur was not accompanied or followed by evidence of pericarditis.

3. It would seem likely that this murmur is pleuropericardial in origin.

REFERENCES

(1) HAMMAN, L.: Trans. Assn. Amer. Phys., 1937, *52*, 311.

(2) NORRIS AND LANDIS: Diseases of the chest and the principles of physical diagnosis, ed. 5, W. B. Saunders Company, Philadelphia, 1933, p. 765.

PROTAMINE INSULIN AND COLLAPSE THERAPY IN DIABETES COMPLICATED BY PULMONARY TUBERCULOSIS[1]

BENJAMIN J. ELWOOD

The association of diabetes mellitus and pulmonary tuberculosis has furnished a problem in combined disease management which, until within comparatively recent years, was not rewarded with encouraging therapeutic results. The universal application of collapse therapy in pulmonary tuberculosis and the use of insulin and correlated dietary advances in the management of diabetes have so favorably altered the prognosis that the application of these measures for both diseases merits continued evaluation. The addition of protamine insulin to the therapeutic armamentarium for diabetes opens a new phase of management, here chiefly concerned with the determination of its value in diabetics with complicating tuberculosis. The above considerations are accordingly stressed in the review of 21 cases included in this report.

The present status of combined therapy is such that the management of the diabetic component offers few problems if it is recognized that meticulous observations of tolerance trends and caloric intake and capacity must be constantly made and determined in relation to the state of tuberculous infection. Finally diabetic stabilization may not be ultimately accomplished until the pulmonary infection is favorably influenced by active means, and this implies that reasonably soon after the diabetes begins to respond specific measures such as collapse therapy, if otherwise indicated, should be applied. The prognosis, however, remains generally poor for the vast majority of reported cases and, in the last analysis, may be attributed to the discovery of a pulmonary process in the far advanced stage and often of the caseous cavernous type in a physically depleted individual usually past the fourth decade. Because of the acute and progressive nature of the pulmonary disease, collapse therapy becomes urgent. Its election moreover is made despite the limitations imposed upon the success of its induction and satisfactory

[1]From The Hudson County Tuberculosis Hospital, Dr. B. S. Pollak, Medical Director, Secaucus, New Jersey.

maintenance. The chief obstacles anticipated are offending adhesions and extensive caseation which interfere with adequate relaxation of pulmonary tissue necessary for effective pneumothorax. In such caseous processes, empyema is more apt to occur; it disturbs the diabetes considerably, and its course is conceded to be more uniformly fatal than in nondiabetics. The more radical procedure of thoracoplasty has been performed relatively rarely and the present status of concurrent disease finds few cases which survive, exhibiting sufficient regression and stability, to permit the more extensive measures.

Since collapse procedures more than any other treatment offer the patient with advanced and progressive tuberculosis greater opportunities for control of his disease, their use in this series of cases was extended more fully as evidenced by the fact that therapeutic pneumothorax was applied in 62 per cent of the cases, a proportion higher than generally reported. Only 2 cases presented minimal lesions, the remainder were moderately or far advanced caseous bronchopneumonic or pneumonic lesions and cavitation of at least moderate size and frequently multiple. Eight patients including the 2 with minimal lesions were carried solely on bed-rest and serve in part as a control group. Therapeutic pneumothorax was induced in the remaining 13, an effective collapse being obtained in 5 (one a bilateral). This closely parallels results in a much larger series of nondiabetics of the sanatorium. In 8 cases pneumothorax was abandoned after a reasonable trial as ineffective, chiefly because of numerous adhesions unsuitable for surgical division. Of this group, one was subsequently able to undergo a two-stage thoracoplasty with an effective result. The remaining 7 were managed on a bed-rest regimen and only 3 have survived, 2 with spontaneous closure of cavities and arrest of the disease. Of a total of 15 cases for which bed-rest was either elected as a single therapeutic measure or enforced because of ineffective and abandoned pneumothorax, a good recovery has been accomplished in 4. If an evaluation be made of the moderately and far advanced lesions, only 2 are well, disclosing a recovery rate of 13 per cent. This may be compared with the collapse therapy group of 13 patients in whom a good recovery (closure of all cavities, arrest of other pulmonary processes, negative sputum, ambulant state) is noted in 6 individuals (46 per cent), 5 by pneumothorax and one by thoracoplasty.

Although the importance of all attempts at controlling the pulmonary disease is reflected in the reduction of the adverse effects of infection upon the diabetes, the utilization of insulin for the stabilization of the

latter is not obviated. The employment of protamine insulin would seem in this brief series of cases to have overcome certain disadvantages still generally existent with plain insulin, the use of which otherwise measurably controls the diabetic derangement despite complication by active pulmonary tuberculosis. The early disclosures of its mode of action and peculiar advantages of administration over unmodified insulin merited its immediate clinical trial in a disease state marked by frequent tendencies to acidosis, shifting tolerance trends and varying capacities of caloric intake. The complication of infection otherwise invokes a need for increased amounts of plain insulin administered in many divided doses to assure maintenance of stabilization. In tuberculosis, where frequent small feedings rather than three main meals are more easily accepted and better assimilated but are disturbing the effectiveness of plain insulin, the employment of the protamine product would seem to promise better results. The preparation certainly merited trial in instances of arrested pulmonary disease where the problem was largely one of residual diabetes. Protamine insulin accordingly was employed in 14 of the 21 patients. In the remaining 7, plain insulin was used exclusively. Observations of its use may be made in the stage of uncontrolled diabetes and active tuberculosis. Early in the course of attempted stabilization a small supplementary fraction of unmodified insulin appeared necessary in some, but eventually a uniform regimen was employed in all, indicating possibly the necessity for employing larger doses than the author was first willing to utilize. Nevertheless, as compared to plain insulin, stabilization was not as rapid nor as complete, and required a total amount of insulin at times almost as large as the plain product. It was at this phase that hypoglycaemic reactions, fortunately few, appeared perhaps more often and dramatically with plain insulin but were more alarming with protamine in that their development was more insidious and their duration more prolonged. They occurred largely in the early hours of the morning and were characterized chiefly by an apathetic, dazed, weakened and anorexic state. Satisfactory control gauged by relative aglycosuria, reduction of excessive hyperglycaemia, tendency to weight stability or gain, constancy of caloric intake and freedom from reactions were accomplished in most patients of this group. In a few control could not be established with greater amounts or divided doses without the advent of reactions described. Utilization of plain insulin resulted in relative stabilization in all cases except for a patient's lack of coöperation. The rôle of such factors as

rapid progression of disease, onset of empyema or dramatic subsidence of activity, which accordingly operate to affect diabetic stabilization either adversely or favorably, did not seem to be reflected as clearly under established protamine control, implying a less firm stabilization by plain insulin. Nevertheless if one considers the manner in which shifting tolerance trends may indicate responses or inadequacies of pulmonary therapy, the more delicate control afforded by plain insulin may be construed as an important clinical adjunct not to be sacrificed.

The use of protamine insulin in a later stage of combined disease management, characterized by established diabetic stability and regressing or therapeutically controlled tuberculosis, displayed a more definite advantage over plain insulin in that the dosage and frequency were significantly reduced; a single injection not exceeding 45 units, administered just before breakfast, often sufficed. The addition of graduated exercise to the regimen however did not reflect the reduced insulin requirement occasionally noted with plain insulin.

In a group of cases, all fully ambulant and with arrest of pulmonary disease either by collapse or routine therapy, the employment of protamine insulin, as was anticipated, was more easily adapted and almost immediate substitution for plain insulin could be made with little sacrifice of diabetic stability. Satisfactory control in this group was attained in all but one, the latter a severe diabetic with hypertensive cardiovascular disease. Phenomena pointing to cardiac anoxaemia developed on dosages necessary to avoid excessive glycosuria and emphasized the danger of correspondingly reducing glycaemic levels below vascular nutritional requirements.

Progressive terminal pulmonary disease featured by physical depletion, little caloric capacity and virtually self imposed starvation could not be evaluated clearly, as the objective findings of the diabetic derangement became progressively less recognizable or even nonexistent. Obviously the small metabolic demands present at this stage were more than adequately covered by endogenous insulin and the use of protamine preparations here proved of no particular advantage as frequently little to no plain insulin sufficed.

Insulin in either form accordingly was employed at some time or another in all cases and gross stabilization of diabetes was accomplished in 16, incomplete or poor control observed in the remainder. Probable causative factors of the latter can be outlined to include lack of coöperation by dietary indiscretions, severe complicating oral and vaginal sepsis

and acute empyema. Where protamine insulin was employed in 14 cases the percentage of control of diabetes did not exceed that with plain insulin, but in a broad comparison was qualitatively better in 7, as good in 3, and worse in one. In 3 more cases of terminal disease its use could not be evaluated clearly. Plain insulin requirements for stabilization ran as much as 80 units in as many as five divided doses and as little as 20 units in two divided doses. The patients under protamine exhibited better management in that the unit quantity and frequency was reduced, no case requiring more than two doses nor more than a total of 50 units.

SUMMARY AND CONCLUSIONS

1. The results of collapse therapy for pulmonary tuberculosis and the use of the newer insulins for the control of diabetes are shown in 21 cases with associated disease.

2. Despite the limitations imposed upon the successful continuance of artificial pneumothorax, the employment of this type of therapy restored more than three times as many to health as did an elected or enforced rest regimen. The percentage of effective pneumothorax obtained parallels results observed in nondiabetics.

3. Protamine insulin utilized in all stages of both diseases in association was as applicable as plain insulin and control could be accomplished as often. It revealed limited advantages over plain insulin in the progressive phases of tuberculosis, greater adaptability and better management in tuberculosis therapeutically controlled or regressing. Its use in diabetes and arrested pulmonary tuberculosis demonstrates its best applicability and its advantages here over plain insulin are comparable to those noted in otherwise uncomplicated diabetes. In terminal pulmonary disease it has little or no application and displays no advantage over plain insulin in the control of the diabetic derangement.

The author wishes to express his indebtedness to Dr. B. P. Potter for his counsel, so cheerfully given during this study.

NONCASEATING TUBERCULOSIS

Case Reports[1]

RALPH HORTON, N. STANLEY LINCOLN AND MAX PINNER[2]

In a recent paper the literature on noncaseating tuberculosis was analyzed. The present report of four cases should serve as an illustration to the conclusion drawn in the former publications (1, 2).

CASE REPORTS

Case 1: Noncaseating tuberculosis (sarcoid type) of skin, lymph nodes, bones and lungs of eleven years' duration; anergy, monocytosis; terminal transformation in necrosing and bacilliferous tuberculosis with allergy; death; autopsy.

Mr. W. B., Mount Morris Tuberculosis Hospital, Mount Morris, New York. On admission to the hospital in August, 1936, this patient was 42 years old. His chief complaint was dyspnoea, cough and gastric distress. His family and past history were not pertinent with the possible exception of tonsillectomy and adenoidectomy in 1916.

This patient dates the onset of his present illness to 1925; before this he had been well. In 1925 he developed enlarged lymph nodes in the neck that were excised in the Lake Avenue Hospital, Rochester, New York. The operative wound healed readily without the formation of a fistula. Shortly following this operation he noticed shortness of breath on exertion, which increased gradually during the next years. At the same time there was a continuous loss of weight. By 1931 he felt chronically ill, but he did not seek medical advice until April, 1933, when he was seen by Dr. Wm. S. McCann in Rochester. His chief complaints were shortness of breath and pain on urination. The latter symptom was caused by a nonspecific anterior urethritis. Guinea-pig inoculation with urinary sediment did not reveal any tubercle bacilli. An X-ray film of the chest at that time showed a considerable involvement of both lungs which was interpreted as tuberculosis, although no acid-fast bacilli were found in the sputum.

In 1934 he developed gastric pain and haematemesis and was admitted to the Strong Memorial Hospital in Rochester with the diagnosis of bleeding

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peptic ulcer. His gastric pain occurred about two hours following meals and at night. These symptoms improved under a Sippy diet and he was discharged after twenty-five days. Urological examination during this period of hospitalization aroused the suspicion of tuberculosis of the urogenital tract, but tubercle bacilli were not demonstrated in the urine.

Starting January 1, 1935, he had a cold with nasal discharge, sore throat and enlargement of a left cervical lymph node. He was readmitted to Strong Memorial Hospital. He had a few excoriated red skin lesions over the maxillae, knees and elbows, none measuring more than 1 cm. in diameter. Several small lymph nodes were in the cervical, right epitrochlear and inguinal regions. Dulness, diminished breath-sounds and posttussive râles were noted over both apices. Roentgenological examination showed progression of the pulmonary lesions, but repeated sputum examination did not reveal any tubercle bacilli. He did not react to an intracutaneous injection of 0.1 mg. of OT. His urine contained some albumin and white cells, but no tubercle bacilli. Phenolsulphthalein excretion was 29 per cent in two hours and urea clearance was 55 per cent in the first hour and 47 per cent in the second hour. There was a moderate secondary anaemia, a white count of 3,400 with a normal differential count. All other laboratory examinations were normal.

On biopsy specimens of a lymph node from the right axilla and of a skin lesion from the right knee the diagnosis of tuberculosis was made. The patient was discharged from Strong Memorial Hospital on January 28 with the following diagnoses: Pulmonary tuberculosis, tuberculous lymphadenopathy, tuberculides of the skin, duodenal ulcer, renal insufficiency, probably due to amyloid disease.

Following this last hospitalization he felt relatively well, although his dyspnoea persisted. In the spring of 1936 he had another cold and since then cough and dyspnoea increased up to the time of his admission to the Mount Morris Tuberculosis Hospital.

On physical examination the emaciated patient appears considerably older than his stated age. On the skin of his upper lip, left cheek, both zygomata, forehead, neck, back and knees, there are multiple slightly raised areas, 4 to 8 mm. in diameter, dark brownish-red, with smooth and shiny surface and sharply defined against the surrounding normal skin. In addition, there are a few depressed atrophic scars of comparable size. The sclerae and conjunctivae are injected and there is some lacrimation and photophobia. All teeth are extracted. Most peripheral lymph nodes are enlarged and palpable as discrete, nonadherent, indolent nodules of rubbery consistence, measuring from 1 to 3 cm. in diameter, the largest ones being in the right axilla.

The respiratory excursions of the thorax are diminished. The percussion note is essentially normal over both lung fields. Over the upper portions of both lungs there is bronchial breathing, and coarse and fine râles are heard

in these regions after coughing. On the left side at the level of the fourth and fifth rib cavernous breathing is heard. Otherwise, the physical examination did not reveal any pertinent findings.

The chest roentgenogram on admission (figure 1) shows disseminated fibronodular lesions in dense seeding throughout both pulmonary fields, decreasing in density in caudal direction. At the level of the first intercostal space, bilaterally, are areas of increased translucency, approximately 3 cm. in diameter, suggestive of cavitation. The hilar shadow is considerably enlarged in the left upper portion of the mediastinum. Both diaphragmatic leaves show some tenting. Later roentgenograms show slow progression of the lesions manifested by more definite excavation in both upper lung fields and intensification of the nodular shadows. A roentgenogram of his hands (figure 5) shows definite cyst-like lesions in the second phalanx of the fourth left finger and in the first phalanx of the first left finger. Less definite lesions of similar character are seen in the first phalanx of the third left finger and in the second phalanges of the first and second left fingers. There are areas of irregular increased density in some of the phalanges. A roentgenogram of his feet does not show any abnormality.

In September he did not react to .000,2 mg. and .005 mg. of PPD, but in November he had a two-plus reaction to .01 mg. of PPD. Sputum examinations by direct smear and concentration in August and September did not show any tubercle bacilli, but in October a concentrated sputum showed tubercle bacilli and yielded a culture of tubercle bacilli. There was an anaemia with 3.5 millions erythrocytes, the total white count was 6,100 and 7,800 respectively, the differential counts were normal with the exception of a monocytosis of from 12 to 15 per cent. He did not concentrate his urine to more than a specific gravity of 1,013 and his urine contained large amounts of albumin, granular casts and white cells. Phenolsulphthalein excretion in two hours was 22 per cent. In October and December his nonprotein nitrogen was 78 and 84 mg. respectively, his urea nitrogen 57 and 54, and at the latter examination his creatinine was 4.8 mg. His highest blood-pressure recorded was 122/80.

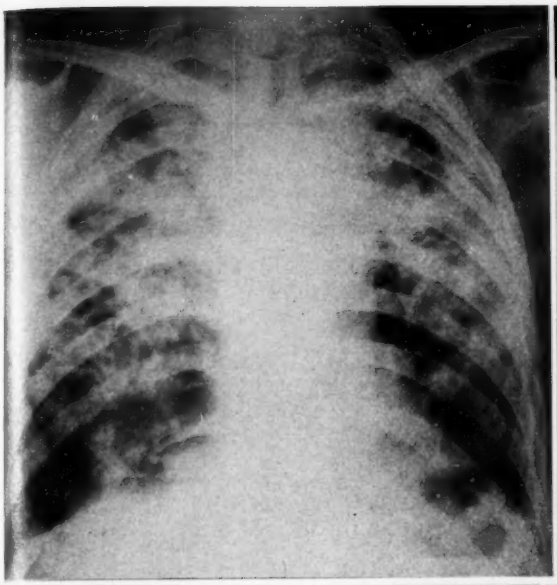
FIG. 1. Case 1. September 23, 1936. Diffuse, essentially fibrotic involvement of both lungs, with cavities in both upper lung fields and emphysema in the basal portions. Bilateral enlargement of the hilar shadows. (Within the stomach bubble, protruding from the midline, the shadow of the enlarged retroperitoneal lymph nodes can be seen.)

FIG. 2. Case 2. November 10, 1936. Diffuse interstitial fibrosis, bilateral.

FIG. 3. Case 3. March 12, 1937. Diffuse, essentially fibrotic involvement of both midportions and the right base; emphysema throughout, but particularly basally.

FIG. 4. Case 4. November 17, 1937. Diffuse interstitial fibrosis, bilateral. Note the close similarity to fig. 2.

FIG. 5. Case 1. The roentgenogram of the hands shows cystic bone lesions in several phalanges of both hands, some marked by arrows.



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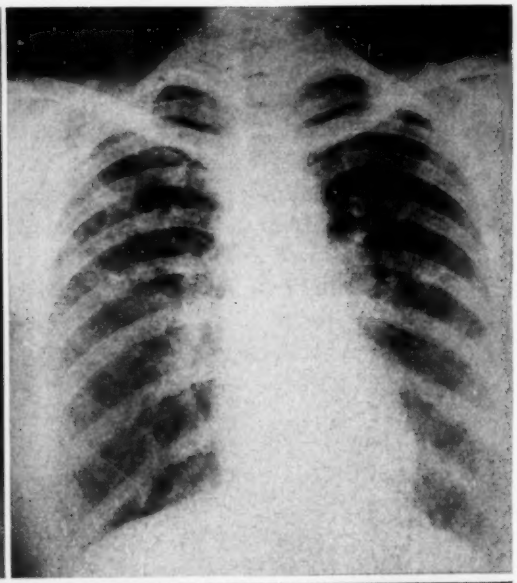

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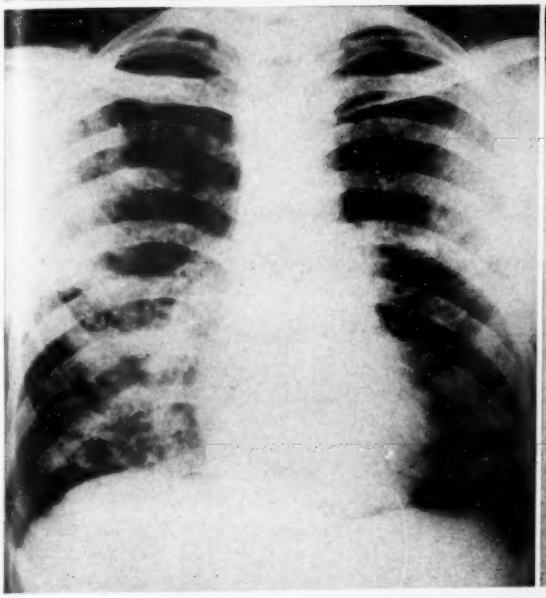

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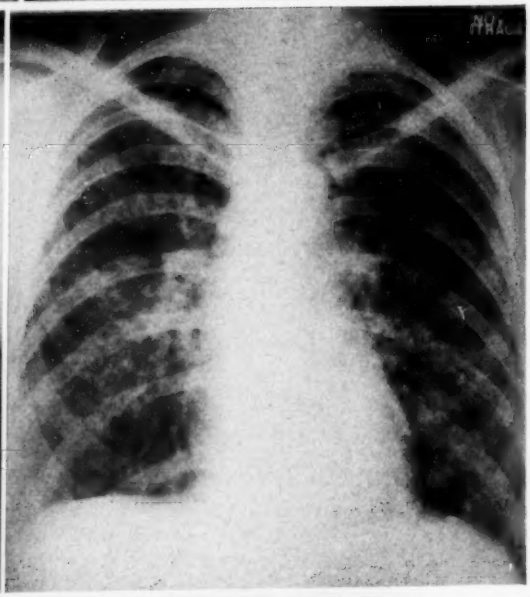

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FIGS. 1-5

On October 6 a submental lymph node and a piece of skin from the right knee were excised for biopsy. The lymph node measures 1 cm. in largest diameter; it is well encapsulated. The cut surface shows firm homogeneous creamy-white tissue. Microscopically it is seen that the normal lymph node structure

FIG. 6. Cut surface of lungs of case 1. Note cavities in shrunken upper lobes, diffuse web-like interstitial fibrosis, small nodular foci and fibrotic pleura.

is completely replaced by nodular accumulations of epithelioid cells, ovoid in shape with vesicular nuclei and pale staining. Narrow strands of lymphocytes surround the epithelioid tubercles. No giant cells and no caseation are seen (figure 8). In the centre of the sections there are areas of pink staining coarsely fibrillar material without nuclei, in shape and arrangement indicating

their development from the tubercles described above (figure 9). Diagnosis: noncaseating tuberculosis (sarcoid type) of lymph node with partial fibrotic transformation.

In the section of the skin (figure 7) the same type of epithelioid tubercles are seen in the derma and peripherally to these tubercles are areas of coarse hyaline fibrosis. Diagnosis: noncaseating tuberculosis of skin (sarcoid type).

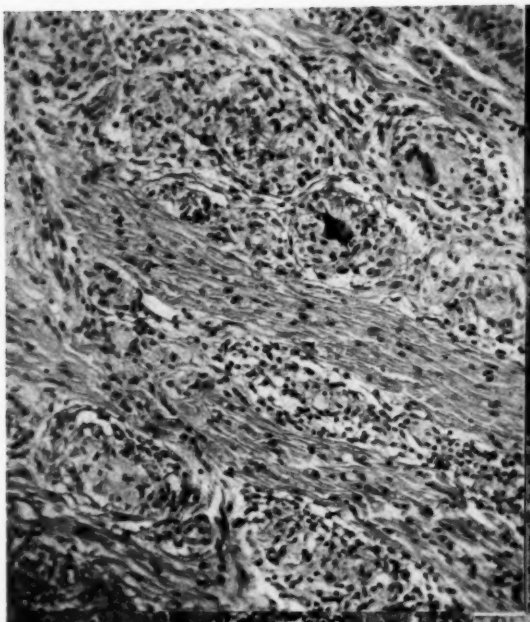
Acid-fast rods are not demonstrable in these lesions. Smears, cultures and guinea-pig inoculations yield negative results.

The clinical course of the patient during hospitalization was steadily downward. Cough and dyspnoea increased. There was occasionally some blood-streaking in his sputum. He complained increasingly of epigastric distress with nausea and occasional vomiting. He had increased urinary frequency up to four or five times per night. His temperature fluctuated between 99° and 101°F., reaching 102°F. several times during the last week of life. With rapidly increasing weakness and dyspnoea, death occurred on December 7, 1936.

Autopsy findings: The body is emaciated and the skin and the visible mucous membranes are pale. The skin lesions are present as described above. There is marked fibrotic pleuritis bilaterally, obliterating the entire right and the upper half of the left pleural space. The lungs are heavy and voluminous. On cut surface (figure 6) the upper portion of each lung is surrounded by a hyaline thickening of the pleura, measuring up to 5 cm. in thickness. Both upper lobes are much decreased in size. In each upper lobe there is an irregular, stiff-walled cavity, approximately 4 cm. in diameter. These cavities are relatively dry and the absence of caseous material is noted. The remainder of the upper and middle lobes shows dense, irregular strands of hyaline fibrosis which in many parts has a slightly bluish tinge. These fibrous changes decrease progressively toward the base of the lungs and reveal their interstitial arrangement. In the lower lobes the hyaline strands follow the interlobular septa, the peribronchial and perivascular tissue and the subpleural layers. The intervening parenchyma is dark brown and shows evidence of vesicular emphysema. Scattered irregularly through the parenchyma are creamy white nodules of firm homogeneous tissue, sharply circumscribed, measuring from 0.5 to 2.0 mm. in diameter. In the anterior portion of the right lower lobe, directly above the diaphragmatic surface is a wedge-shaped area with its broad surface toward the pleura, measuring 2 x 2 x 7 cm. and consisting of dry, firm, grayish-white apparently caseated tissue. Embedded in the thickened pleura are a few nodules of firm, dry caseated material.

Similar firm nodules are found in the epicardium and projecting into the underlying myocardium, in the liver, in the spleen and in the kidneys.

There is a localized hyaline thickening of the splenic capsule.



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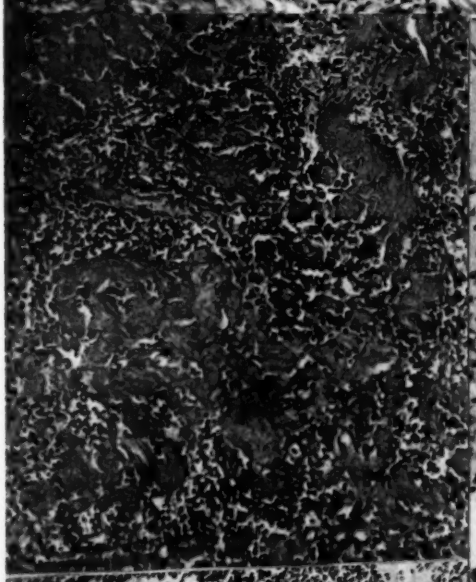

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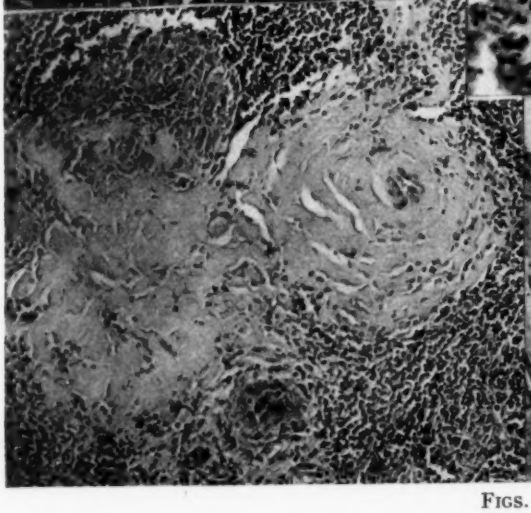

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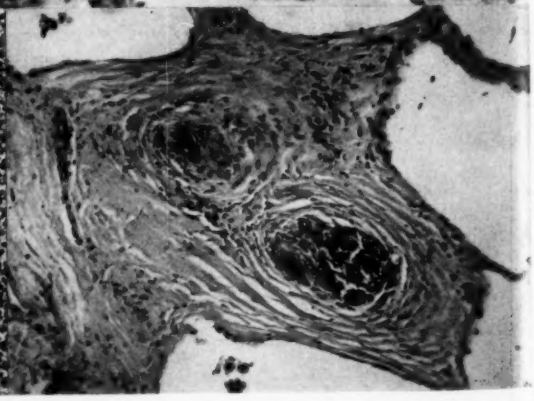

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FIGS. 7–12

The following lymph nodes are enlarged: axillary, supraclavicular, anterior cervical, paratracheal and peribronchial, periaortic, retroperitoneal and mesenteric. The cervical and mesenteric lymph nodes are moderately enlarged, up to 2 cm., and their cut surfaces show a homogeneous slightly pink tissue. The axillary lymph nodes, measuring up to 5 cm., are much harder and show on cut surface a mottling of cream and gray. Some of the axillary, the perihilar and the retroperitoneal lymph nodes contain many small areas of yellowish firm tissue which is thought to be caseated. The largest lymph nodes are in the retroperitoneal space at the level of the stomach; the largest single node measures 8 cm.; but in this region many nodes are matted loosely together, forming a mass the size of a man's fist. This mass is adherent to the posterior wall of the stomach near the lesser curvature, and, on opening the stomach, it is found that this parcel of lymph nodes bulges deeply into the lumen of the stomach. But the gastric wall itself appears normal. The hilar lymph nodes are very firm, and those below the bifurcation contain a few small hard calcified foci.

The only other pertinent finding refers to the kidneys. They are reduced in size, weighing 81 and 83 gm. respectively. The capsules on stripping tear the parenchyma and leave slightly and finely granular surfaces. The surfaces are pale grayish-red with many 1 to 2 mm. nodules of cream color slightly bulging over the surface. On cut surface the cortical layers are reduced to a thickness of from 1 to 2 mm. and they are pale red. The pyramidal markings are less distinct than usual. There are many small nodules visible, similar in appearance to those seen on the surface.

No evidence is found for an active or healed ulcer in the gastric or duodenal mucosa.

The cranial contents do not show any abnormality.

The second phalanx of the left little finger and the peripheral third of the proximal phalanx of the left index finger are removed for histological examination; they do not show any gross abnormality.

Histological examination: Lungs: sections through the cavity walls show an almost completely hyalinized fibrous tissue consisting of particularly broad fibrils, concentrically arranged around the lumen of the cavity. There is an unusually thin inner layer of granular necrosis in which an occasional acid-fast rod is found. In many of the sections, the hyaline fibrosis and emphysema are the outstanding features (figure 13); it shows the distribution indi-

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FIG. 7. Epithelioid tubercles with few giant cells in cutis. H.E.

FIG. 8. Epithelioid tubercles in lymph node. H.E.

FIG. 9. Fibrosed tubercles in lymph node. Note coarse fibrillar structure. H.E.

FIG. 10. Epithelioid tubercles in lung. H.E.

FIG. 11. Two small epithelioid tubercles and two larger fibrotic tubercles in spleen. H.E.

FIG. 12. Epithelioid tubercles, surrounded by hyaline fibrosis, in lung. H.E.

cated by the gross appearance. In many regions this hyaline tissue stains light orange with van Gieson. The single small nodules are accumulations of epithelioid cells; some show epithelioid tubercles (sarcoid structure) (figure 10) and in them acid-fast bacilli are not found; others show central granular necrosis and here acid-fast bacilli are demonstrable; still others, probably the majority of them, are surrounded by hyaline fibrosis (figure 12). Many of the tubercles are found lining the broad hyaline bands. Elastica stains fail to demonstrate any elastic fibres within the granulomatous lesions or within the hyalinized tissue. The large caseated area in the right lower lobe shows complete necrosis in which, however, the pulmonary structure is still faintly visible. The necrotic tissue is less homogeneous and contains more nuclear debris than is usually seen in caseous pneumonia. Elastic and connective tissue stains bring out clearly alveolar walls, blood vessels and bronchi.

The other involved organs, lymph nodes, kidneys, liver, spleen, epicardium, adrenals and bone marrow, show any or all of the three main lesions: epithelioid tubercle, epithelioid tubercles with more or less complete necrosis and fibrosed and hyalinized tubercles. Only in the tubercles showing definite necrosis were tubercle bacilli demonstrable. Pure epithelioid tubercles are seen, in addition to the lungs, in the spleen (figure 11), kidneys, adrenals, in cervical and some mesenteric lymph nodes. Necrosed tubercles are found in the kidneys, spleen, liver, many lymph nodes and epicardium. Fibrosed and hyalinized tubercles are present in many lymph nodes, particularly in the perihilar region and in the retroperitoneal space, in the spleen (figure 11) and in the lungs.

Sections through the phalanges (figure 14) and through the bone marrow of the *manubrium sterni* show that the cortical bone is essentially normal, that the bony trabeculae of the marrow cavity are either thinned out considerably or have disappeared. There are many more or less fibrosed granulomata in which the fibrosis has a much finer fibrillar structure than in the other organs. Only in one section from the left little finger is the cortex replaced by a fibrogranulomatous focus, extending from the marrow cavity into the soft tissue.

In the kidneys there are found a moderate number of miliary caseated tubercles and, particularly in the medullary portion, a few epithelioid cell granulomata. In addition to these specific lesions, the kidneys show distinct degenerative changes in the epithelial cells of the proximal convolutions; these changes consist of globular degeneration, swelling, some loss of nuclei, granular and homogeneous casts; other tubules are entirely shrunken and completely replaced by calcified globules, similar to *corpora arenacea*. The latter change is focal in distribution, particularly in the subcapsular zone. Some of Henle's loops contain similar casts as the convoluted tubules, in places intermingled with a few polymorphonuclear leucocytes. A few collecting tubules contain a leucocytic exudate. Only the larger arteries show

FIG. 13

FIG. 14

FIG. 13. Hyaline fibrosis and emphysema of lung. H.E.

FIG. 14. Section through the second phalanx of the left fourth finger, showing replacement of bone marrow by fibrosed granulomata and disappearance of the bony trabeculae. Mallory's aniline blue.

moderate hyalinization and thickening of the intima, but no narrowing of their lumina. Some glomeruli have thickened capsules, but their capillaries are intact. In the cortex are a few scars with many hyalinized glomeruli and marked lymphocytic interstitial infiltration.[3]

Case 2: Tuberculous uveitis; noncaseating tuberculosis (sarcoid type) of lymph nodes, proved by biopsy; disseminated pulmonary lesions, asymptomatic; low-grade allergy; monocytosis; anticutins.

Mrs. E. W., Homer Folks Tuberculosis Hospital, Oneonta, New York. At the time of admission in June, 1936, this patient was 35 years old, a white school teacher of Swedish-German descent; she had been married five years, had no children but had had two abortions, in 1933 and 1934, respectively. She was referred to this hospital on account of roentgenologically demonstrated pulmonary lesions.

Her past history is not pertinent.

Her present illness started with burning and aching of her eyes in the fall of 1933. These symptoms disappeared within three months, but in the spring of 1934 her vision began to decrease and black lines and spots appeared in her visual field. These symptoms did not abate under medical care, and in the fall of 1934 it was decided that some focus of infection might be their cause and, therefore, several abscessed teeth were extracted and her right maxillary antrum was curetted. In the spring of 1935 two more teeth were removed and tonsillectomy and adenoidectomy were performed. By September, 1935, her right eye had improved but her left eye was worse. In May, 1936, a diagnosis of ocular tuberculosis was made. She was, then, hospitalized for one week in the Presbyterian Hospital in New York where a diagnosis of tuberculous uveitis was made by Dr. John M. Wheeler. On account of this diagnosis a chest roentgenogram was made which was interpreted as showing pulmonary tuberculosis; therefore, sanatorium treatment was recommended.

On admission, the patient complained of pain in her eyes and failing vision, the left eye being more severely affected than the right. In addition she noticed some fatigue. She had no cough and no expectoration, but she was aware of some dyspnoea on exertion during the last three years. She stated that she perspired freely when excited, but that she never had any night sweats. She had noticed a fine tremor of the extended hands for the last six or eight years. Her appetite was good and she had gained some weight during the last year. Her pulse rate varied greatly between 60 and 120 per minute.

The pertinent findings on physical examination were as follows: She is a

[3] We are greatly indebted to Dr. Kornel Terplan for his most valuable advice in the interpretation of the histological picture of the kidneys.

well nourished woman who does not give the impression of being ill. In the anterior cervical triangles and in the supraclavicular fossae are a few enlarged lymph nodes, measuring up to approximately 1.5 cm. in diameter; they are of rubbery consistence, freely movable and apparently not adherent to the surrounding structures; the largest ones are palpated in the right supraclavicular fossa; all these nodes are not tender. In no other region are lymph nodes palpable.

There are dulness and somewhat diminished breath-sounds over both apices; otherwise the lungs do not present any abnormal physical signs.

Ophthalmological examination (Dr. D. F. Gillette) July 16, 1936: Right eye: Some fine *keratitis punctata* on Decimet's membrane; few cells in the anterior chamber, several nodules on the pupillary edge of the iris; few vacuoles in the lens; some fine vitreous opacities and multiple lesions in the choroid, in the lower half, these also involve the retina over them. The lesions of the choroid are very suggestive of tuberculosis. The vision in this eye is 20/20. Left eye: Mild ciliary injection; there are many large mutton fat *keratitis punctata* on Decimet's membrane and many cells in the anterior chamber; the iris is hazy and vascularized and has several medium sized tumors, which have the appearance of tubercles. The pupillary margin is bound to the lens, and the pupillary area is filled in with exudation. The vision in this eye is fingers at one foot distance. The process in this eye looks like tuberculosis.

The remainder of the physical examination does not reveal any abnormality.

Serial chest roentgenograms taken at monthly intervals between July, 1936 and January, 1937 all show essentially the same condition without any noticeable change. There is a symmetrically distributed mottling of moderate density, practically throughout both pulmonary fields, more definite and denser in the upper thirds and in the perihilar regions. The individual shadows consist more of stippling and linear markings than of nodular formations. The hilar shadows are fairly heavy, but probably still within normal limits. Otherwise, these roentgenograms show no abnormality (figure 2). The roentgenological findings are interpreted as diffuse fibrous changes following haematogenous dissemination. They are consistent with the diagnosis of pulmonary sarcoid. Roentgenograms of hands and feet do not show any lesions.

Graded intracutaneous injections of OT elicit a one-plus reaction to 1.0 mg.

Laboratory findings: There is a mild hypochromic anaemia. The total white count fluctuates in sixteen examinations between 4,500 and 6,250. The differential counts are essentially within normal limits, except that in nine out of sixteen counts the percentage of monocytes is between 8 and 12 per cent. All other laboratory examinations are negative.

On July 14, 1936, several lymph nodes were excised from the right supra-

clavicular fossa for histological and bacteriological study. The largest node measures 1.2 cm. in diameter. The nodes are well encapsulated, moderately firm and, on cut surface, show a homogeneous cream-colored medullary tissue without focal lesions. On microscopical examination it is found that the normal structure is completely replaced by globular accumulations of large, pale staining epithelioid cells with faintly staining vesicular nuclei. These epithelioid-cell tubercles, measuring one-half to one low power field in diameter, contain only a rare Langhans' giant cell and there is no caseation or necrosis. The tubercles are surrounded by thin layers of lymphoid cells. Intensive search for acid-fast rods remains unsuccessful. Cultures from these lymph nodes remain sterile, and guinea pigs injected with the material did not develop tuberculosis. These findings are characteristic of sarcoid.

The blood serum of this patient contains tuberculin-neutralizing substances. A more complete discussion of this finding is presented following the case reports.

During her stay in the hospital she received, upon ophthalmological advice, a course of tuberculin treatment. Occasionally she developed a slight local reaction. Otherwise, her course was uneventful; her ocular condition remained essentially unchanged and, as mentioned above, her pulmonary condition never gave rise to symptoms except for slight dyspnoea on exertion, and remained stationary according to roentgenological evidence. No fresh lymphadenopathy developed during the period of observation and there never were any cutaneous lesions.

Case 3: Noncaseating tuberculosis (sarcoid type) of peripheral lymph nodes (duration about four years) and of lungs (unknown duration) with secondary emphysema, anergy.

Mr. E. C., Mount Morris Tuberculosis Hospital, Mount Morris, New York. This patient, a 31 year old, white, married railroad worker, was admitted to the hospital on March 10, 1937.

At the age of 16 he had rheumatic fever and was confined to bed for several months. Otherwise his past history and family history are unessential.

His present illness started probably three years ago with a painful swelling in his left axilla which grew to the size of a hen's egg and then slowly receded to one-third that size. Otherwise he felt well until about one and a half years ago. At that time, in the fall of 1935, he developed a severe cold and pain in his left chest. Although he stayed in bed repeatedly for a week or so, his symptoms increased. In January, 1937, he came to one of our travelling clinics where he was advised to enter the hospital. He finally stopped work in February, 1937 and was admitted to the hospital on March 10, 1937.

On admission he complained of cough, expectoration, amounting to about 20 cc. a day, occasional chest pains and some loss of weight. Four years ago

he weighed 155 pounds, now his weight is 143 pounds. During the last year his ankles were swollen at times and he had urinary frequency and nocturia.

On physical examination no skin lesions are seen. In the cervical region there are a few shotty lymph nodes. In the left axilla are multiple swollen nodes, the largest about 3 cm. in diameter; similar but somewhat smaller nodes are palpable in the right axilla, one in the right epitrochlear space and about five fairly large ones in each inguinal region. There is a moderately severe conjunctivitis. The thorax is symmetrical, but the respiratory expansion is somewhat limited and the diaphragmatic excursion is decreased on both sides. Tactile fremitus and percussion note are normal. The breath-sounds are diminished over both lungs and accompanied by inconstant musical râles. From the level of the fifth posterior rib to the base there are crepitant and fine crackling râles, extending into the axillary regions and anteriorly to the bases. Whispered voice and vocal fremitus are normal. The blood-pressure is 120/82. The remainder of the physical examination does not reveal any abnormality.

Intracutaneous tuberculin tests up to 1.0 mg. OT remain negative. His vital capacity is 2,660 cc., that is, about 60 per cent normal.

Repeated sputum examinations, including two cultures, fail to show acid-fast bacilli. Repeated blood counts are essentially normal with the exception of a monocytosis of 9 per cent on two occasions. The urine is normal.

The chest roentgenogram on admission (figure 3) shows dense minute stippling between the second and sixth rib on the right side extending into the cardiophrenic angle, and between the first and sixth rib on the left side. On first glance one receives the impression that these areas show diffuse infiltration, but on closer inspection it is seen that the shadows consist of minute nodular lesions. A roentgenogram taken fourteen months later shows definite regression: there is some resorption, particularly in the peripheral zones of the involved areas, the stippling is less dense and there are now more fine linear markings instead of the minute nodulation in the first roentgenogram. Roentgenograms of hands and feet show normal conditions.

In the middle of April, 1935, one epitrochlear lymph node, five left axillary nodes and one right inguinal node (largest diameter 2 cm., 4 cm. and 1 cm., respectively) were excised. Smears and cultures from these nodes do not reveal any acid-fast bacilli. The nodes are firm, completely encapsulated and homogeneous, grayish-white on cut surface. Histologically, these nodes present exactly the same picture as those biopsied in case 1. There is the same mixture of epithelioid cell tubercles and fibrotic-hyalinized nodules.

During the period of hospitalization from March 10 to May 27, 1937, the temperature ranged between 98° and 100.4°F. His cough decreased, the sputum became scanty and mucoid. His weight decreased to 133 pounds, but he felt definitely better. A follow-up examination was done one year following

discharge: the patient has further improved subjectively, he has gained weight up to 150 pounds, claims to have no sputum, very little cough and only occasional pain in the chest. His peripheral lymphadenopathy is essentially unchanged and physical examination of his lungs reveals no noticeable change. The roentgenological changes are described above.

Case 4: Noncaseating disseminated tuberculosis of lungs (sarcoid type) of at least six years' duration, preceded by bilateral iritis, tuberculin anergy, asymptomatic.

Miss M. A., Hermann M. Biggs Memorial Hospital, Ithaca, New York. The chest roentgenogram of this patient was seen at a routine examination, but the patient was never hospitalized. The patient is a nurse, 34 years of age, subjectively in excellent health and free of any symptoms of disease.

Past and family histories are not pertinent.

While in training school an X-ray film of her chest was taken in 1928; since nothing was said about this, it may be assumed that it was normal; the same is apparently true of a roentgenogram taken in March, 1929. In June, 1930, she developed iritis in the right eye and was hospitalized for three weeks. In August, 1930, iritis of the left eye developed, and at that time a tonsillectomy was performed. She had an uneventful recovery. A routine roentgenogram in November, 1934, showed scattered lesions; this finding caused a recheck of a roentgenogram taken in October, 1932 and it was stated that this film showed the same lesions. The patient states that the roentgenological findings caused the differential diagnostic consideration of miliary tuberculosis, fungus infection and silicosis. At that time she felt perfectly well and in particular had no symptoms referable to her respiratory system. But she was advised to take an extended rest and she stayed in a sanatorium from December, 1934 to August, 1935, and did not return to work until June, 1937, although she felt entirely well during all this time. At present she is on full-time nursing duty and leads a normal life, including considerable walks. In November, 1934, she did not react to 1 mg. of OT and in January, 1935 she was negative to the two customary doses of PPD.

She first was seen by us in November, 1937. At that time she was of normal weight, well nourished and made the impression of a person in perfect health. Physical examination did not reveal any abnormality, and it was not suspected that she had any pulmonary lesions. She had no skin lesions and there were no palpable lymph nodes.

A chest roentgenogram in November, 1937 (figure 4) shows symmetrically distributed shadows throughout both lung fields. These shadows are rather densely and fairly evenly scattered, somewhat less so in the apical portions. The shadows form a network of stringy markings and there are no nodular infiltrations. The right diaphragm is slightly tented and the hilar shadows appear to be within normal limits. A second roentgenogram was taken in June,

1938; this did not show any change from the previous one. Through the courtesy of Dr. J. R. Byers in Montreal, the serial films, going back to November, 1934, were available for comparison; throughout this period of nearly four years no definite changes have taken place in the roentgenological findings. X-ray films of her feet and hands do not show any cystic changes in the small bones.

The patient's vital capacity is 90 per cent of normal. Her blood picture is normal. Tuberculin tests, done in April, 1938, remained negative up to 1.0 mg. of OT. Her blood serum contains anticutins (see below), but in appropriate tests no bacteriostatic action on tubercle bacilli is demonstrable (Frank G. Petrik).

ANTICUTINS

It has been mentioned (2) that in some patients with sarcoid lesions procutins and anticutins are demonstrable in the blood serum. In

TABLE 1

Area of infiltration in mm., forty-eight hours following the intracutaneous injection of 0.1 cc. OT and OT plus serum into allergic individuals, to demonstrate anticutins in the serum of patients with noncaseating tuberculosis

CASE	OT	SERUM			
		OT plus saline equal parts	OT plus serum equal parts	OT plus 1:10 serum equal parts	OT plus 1:100 serum equal parts
2	1:5,000	20 x 17	15 x 14	5 x 6	
3	1:5,000	14 x 10	1 x 1	2 x 2	3 x 3
4	1:1,000	20 x 20	10 x 5	15 x 10	

mixtures of serum and tuberculin, procutins enhance, anticutins neutralize the skin-reacting factor in tuberculin.

The serum of three of our four patients was studied for such action. The serum was mixed with equal amounts of OT, using undiluted serum, serum diluted 1 to 10, and in case 3, 1 to 100. These tuberculin-serum mixtures and tuberculin-saline mixtures of equal strength were incubated at 37°C. for two hours; 0.1 cc. of each mixture was injected intracutaneously in a known allergic person. The results are summarized in table 1. It is seen that all three sera depressed the skin reaction to a considerable degree. The true significance of this finding needs further study on larger numbers of patients.

COMMENT

In three cases (1, 2, 3) the diagnosis of noncaseating tuberculosis was established by bioptic findings. The histological appearance of the

biopsies in each case was characteristic of Boeck's sarcoid; the diagnostic criteria of this disease and the opinion that Boeck's sarcoid is a non-caseating phase of tuberculosis are discussed at some length in previous publications (1, 2) to which the reader is referred. Case 1 is a typical representative of that group of patients who, after years of the non-caseating phase, finally develop caseating lesions. This case shows the close association of tuberculin anergy with the noncaseating phase and tuberculin allergy with the terminal caseating and destructive phase. The causal relation of these phenomena is a matter of speculation. A fuller discussion of this question will be found in a previous paper (2). According to clinical observation, sarcoid lesions have a tendency to recurrence, each recurrence representing probably a period of haematogenous dissemination. Such repeated seedings are well illustrated in this case by crops of tubercles of apparently different ages (figures 7 to 12).

His renal condition is of some interest: albuminuria with casts, white cells and nitrogen retention, without oedema and with normal blood-pressure. The occurrence of pus may well be related to the breaking down of the specific lesions. Otherwise the morphological picture presents essentially tubular, degenerative disease. The foci of calcification would suggest an increased mobilization of calcium; this is most likely explained by the specific lesions in the bone marrow. The fact that the latter were present not only in phalanges but in the sternum as well, makes it likely that a sufficient number of them was disseminated to cause a considerable calcium mobilization.

Some of the patient's gastric symptoms were probably caused by the mass of swollen lymph nodes, encroaching upon the lumen of the stomach, but it is questionable whether this explains his haematemeses.

Cases 2 and 3 are representative of patients who are apparently in the active stage of noncaseating tuberculosis, as indicated by symptomatology (active uveitis in case 2, fever in case 3, and monocytosis in both and by the histological appearance of the lymph nodes). In these cases it appears justified to assume that the pulmonary lesions were of the same morphology and aetiology as those in the lymph nodes. In both cases, however, the anatomical extent of the disease was out of proportion with the relative paucity of the symptoms referable to the lungs. This discrepancy between anatomical extent of involvement and symptoms is particularly striking in patient 4, who is probably in a non-active stage of the disease. The diagnosis in this case cannot be proved

absolutely, since no foci are available for bioptic study. The diagnosis is made by exclusion and analogy. This patient is probably a good example for those cases in which a diagnosis must and can be made without the absolute proof of histological study. The supporting evidence is seen in the type of roentgenological findings that are not explainable by any other aetiology, its similarity to other pathologically proved cases, its amazing stability over a period of six years, the absence of symptoms and signs, the preceding uveitis, the tuberculin anergy and the demonstration of serum anticutins.

The eventual development of sarcoid lesions is represented in this group of four patients as follows: Case 1 demonstrates the development of noncaseating tuberculosis into caseous, ulcerative tuberculosis, a transformation that has been described repeatedly. Case 3 shows evidence of retrogression, a development that may, according to some reports in the literature, proceed to complete roentgenological clearing. Cases 2 and 4 are apparently in a rather stable phase; they may eventually resorb, or they may go on to increasing fibrosis and emphysema, unless they take a course similar to case 1.

SUMMARY

Four patients with noncaseating tuberculosis (type: Boeck's sarcoid) are reported. In one case the autopsy findings are presented; this patient showed a transformation from noncaseating lesions during a long anergic phase to caseating lesions with allergy.

In two other patients, the diagnosis was confirmed by histological evidence.

In the fourth patient the diagnosis was made by exclusion and analogy, supported by a number of suggestive features.

In the three patients in whom such studies were done, anticutins were demonstrated in the blood serum.

All four patients had, at least temporarily, apparent tuberculin anergy.

REFERENCES

(1) PINNER, M.: Noncaseating tuberculosis, A preliminary report, Amer. Rev. Tuberc., 1937, *36*, 706.

(2) PINNER, M.: Noncaseating tuberculosis, An analysis of the literature, Ibid., 1938, *37*, 690.

SECTIONAL ROENTGENOGRAPHY OF THE CHEST[1]

CLARENCE J. ZINTHEO, JR.

Sectional roentgenography is an application of radiography whereby the rays are, in effect, focussed upon a plane or thin section of the body with the shadows of objects outside of the plane blurred to a greater or lesser degree. The principle of the method was independently discovered by a number of investigators who coined different terms to describe their invention and so the different types of apparatus for accomplishing sectional roentgenography are to-day known under such terms as the tomograph, the stratigraph, the planigraph and the laminagraph. A careful historical résumé and a theoretical analysis of the methods have been prepared by Andrews (2).

Kieffer (4) has given a splendid explanation of the principles involved and has indicated some of the extensions and possibilities opened up by this new method of applying roentgen rays. Since his paper should be carefully studied by all who are interested in the use of sectional roentgenography the theoretical principles will be only briefly presented here. The rays are "focussed" by moving the tube and the film in opposite directions during the exposure at a travel ratio which remains constant. The beam of rays from the tube T (figure 1) passing through the object B will cast its shadow on the film F at the point X. Consider this line TBX to represent also a rigid lever connecting the tube and film and having its pivot at B. If now the tube is moved from T to T′ the film will move in the opposite direction from F to F′, but the beam of rays from the target which passes through B will strike the same spot on the film. If the ratio of the distances TB to BX remains constant, the shadow of B will fall on the same point X for every position of the film from F to F′ and so a sharply defined shadow of B will appear on the film even though the system moves during the exposure. If the film maintains its plane during movement, and does not rotate on an arc, all objects in the body which lie in the plane of the pivot KBL parallel to the film will also be sharply defined. However, another object A in the body outside of this plane, which casts its shadow at M on the film at the initial

[1] From the Firland Sanatorium, Richmond Highlands, Washington.

position, will appear in the final position at the different point M′; that is, the shadow M will move on the film with respect to X. Since X is constant and a sharply defined shadow, M is blurred out and will not be seen. The point A may be taken anywhere above or below the plane KBL. Consequently only the shadow of objects in the plane KBL will be sharply defined and objects above and below this plane will be blurred out to a greater or lesser degree.

Thickness of the body section which will be sharply defined will depend upon the amplitude of movement from T to T′ and the distance of B from the film; in practical sectional roentgenography by any of the

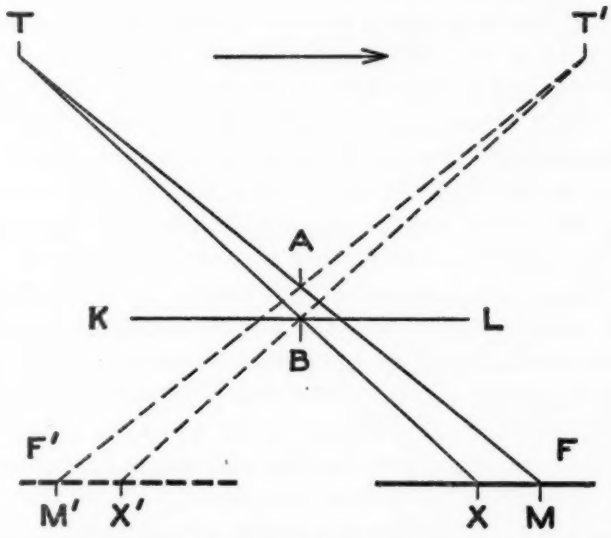


FIG. 1. Fundamental principle of sectional roentgenography. For explanation see text

various methods available it is quite easy to limit this thickness to less than 0.5 cm., and a sharply defined section only 1.0 mm. thick is not difficult to achieve. The location of the plane KBL above the film may be varied by changing the ratio of the distances TB to BX, that is, by setting the pivot point B closer to, or more distant from, the film. In sectional roentgenography of a localized area of the chest a series of films may be made with a separation between the layers of 1 cm., 2 cm., or whatever is desired.

Within the past few years a machine of foreign manufacture for taking sectional roentgenograms has been offered for sale in America under the

trade name "planigraph." Recently the production of Kieffer's laminagraph has been undertaken by an American concern. Because of the expense of these machines, however, sectional roentgenography might be limited to a few financially favored centres were it not that simple attachments to the ordinary Bucky diaphragm table have been described by Twining (8) and by Alexander (1) which permit the making of reasonably satisfactory sectional roentgenograms. It should be understood that such attachments, being hand operated and being limited to a simple longitudinal movement, cannot be expected to give as refined results as the carefully constructed automatic machines which permit a selection of complicated movements best fitted for the study at hand. It happens, however, that the longitudinal movement is reasonably satisfactory for study of the chest and with the attachments described costing so little the use of sectional roentgenography becomes available to many sanatoria and clinics which could not afford the more elaborate equipment.

The essential requirements for sectional roentgenography are: first, the film, in whatever part of the travel it may be, must always remain parallel to every other position; second, the tube and film carriage must be linked by a rigid system so that they move in opposite directions; third, the relative displacement of each, that is, the ratio of the distances TB to BX, must remain constant during the exposure; and fourth, the object must remain stationary and in such a position that the pivot point B or its equivalent lies in the section that is desired to portray. In the ordinary Bucky table, the Bucky can be moved lengthwise with the table beneath the patient and the film will remain in a constant plane. The tube can be moved on its rails in a plane parallel to that of the film. It only requires that the tube and Bucky be connected by a system so designed that when the tube column is pulled the Bucky will move in the opposite direction at a rate that will fulfil the requirements for sectional roentgenography. An obvious method of doing this is a vertical rod running from the tube arm to a projection attached to the Bucky and having an adjustable pivot a little above the table top rigidly fastened to the table edge. This is satisfactory but because the details of such construction present certain problems it is somewhat easier to use a different method of connection in which the system lies in a horizontal instead of a vertical plane.

Alexander's method is based on a system of pulleys, and in this the focal plane is determined by the number of pulleys and the target film distance. Altering the number of pulleys changes the focal plane by

large steps, while focus upon intermediate planes may be obtained by precalculated elevations of the X-ray tube. Such a system of pulleys is perhaps the simplest and least expensive method of securing sectional roentgenograms by attachments to the tube column and the Bucky diaphragm. Variations in the exposure technique required by shifting the target film elevation would be a bother which some might be willing to tolerate if they find difficulty in obtaining the critical piece of the lever arrangement, a well designed and machined adjustable fulcrum.

Twining's method consists of a rigid lever extending across one end of the table in a plane parallel to the table top (figure 2) one end of which is connected by a rod to the tube carriage and the other by a similar rod to the Bucky carriage. A fulcrum, adjustable across the length of the

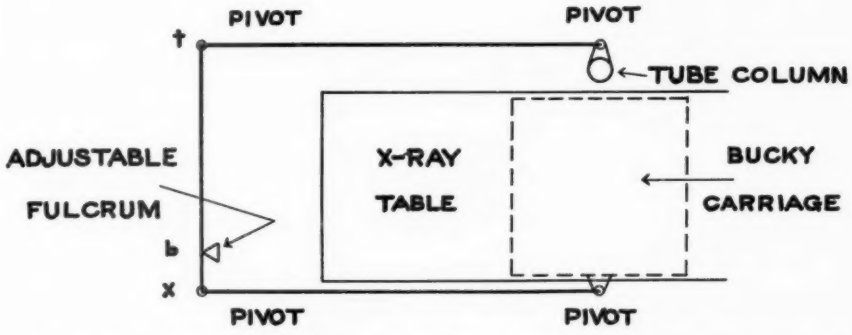


FIG. 2. Diagrammatic representation of Twining's attachments to the Bucky table for securing sectional roentgenograms.

lever, is supported by rods clamped to the table (not shown in this figure). If the tube column be pushed along its rails the movement will be transmitted through the lever and connecting rods to impart a proportional and opposite movement to the Bucky, thus completely satisfying the requirements for sectional roentgenography. The ratio of movement of tube to film will be equal to the ratio of the distances tb to bx; by moving the fulcrum b closer to or more distant from x, the ratio is changed and hence the height above the film of the sharply defined plane will be changed. If the length of the lever tx be made the same as the vertical focal film distance, then the length bx from the fulcrum to Bucky connecting rod will be equal to the height of the sectional plane above the film. Since the distance from film to table top is fixed, it is easy to calibrate the lever by appropriate marks so that the exact

height of the sectional plane above the table top may be predetermined. Completed attachments are shown in figure 3.

The arrangement is operated by hand although it should not be difficult to arrange a motor or water-pressure drive and suitable electric relays to activate the Bucky and the X-ray tube. In use, the patient is placed on the table with the region to be studied directly on the line

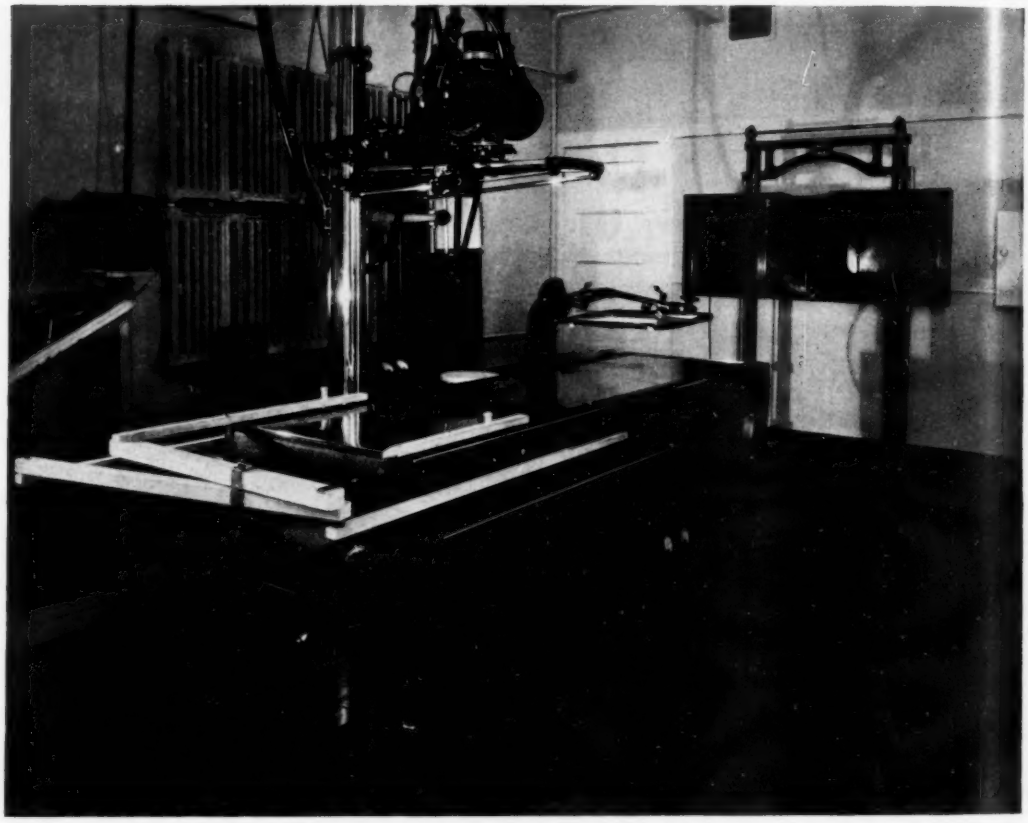


FIG. 3. Twining's attachments as installed

connecting the focal spot and the centre of the film, the adjustable fulcrum is set to the first depth, and the tube column is displaced toward the end of the table. While the patient holds his breath the technician pulls the column at a smooth, slow, even rate toward the other end of the table. An assistant activates the Bucky release when the column is well started and as it crosses a previously located mark on the rails, the Bucky in turn activates the relay switch of the X-ray tube.

A tube film elevation of thirty-six inches may be conveniently used, although any greater elevation up to the limit of the installation may be adopted. A total travel of the tube column of about twenty inches will easily allow a travel of about twelve inches during the time the X-ray exposure is on. With an amplitude of movement of this degree a sharply defined section about 2 mm. thick may be obtained. The regular timer is used for a three-second exposure but with skill the rate of travel can, if desired, be increased and the time of exposure shortened (with corresponding increase of milliamperes). Without a reliable motive power and automatic relays to release the Bucky and activate the X-ray tube, troubles may occur at greater speeds, but, when so improved, it should be quite easy to use exposures of less than one second.

To increase the sharpness of detail of the chosen plane it is necessary to use the smallest available focal spot; a one millimetre focus X-ray tube is preferable. It is essential that the tube axis be oriented across the length of the travel, for, if the axis be in the same direction as the travel, the effective focal size will vary from a very large dimension at one end to a small one as the principal ray approaches the heel of the target at the other end of the travel, with a resulting unnecessary blur of the sectional plane. At normal chest voltages from twenty to one hundred milliampere-seconds will be required depending upon the density of the lesion in the region of interest. The exposure varies from one equal to that which would be given for a normal film with appropriate changes for the closer distance and use of the Bucky, to as much as double or triple that exposure. A previous trial on a small film at what is judged to be correct will serve as a guide for such modifications as may be required. Where the study is made for the analysis of a localized region, such as in the presurgical mapping of cavities, a small film will suffice and it is frequently possible to use an area as small as half of an 8 x 10 plate so that, even when the planes are sectioned every centimetre or half inch from the front to the back of the chest, the cost of materials is less than for a pair of stereoscopic films.

The value of sectional roentgenography is twofold: first, it permits a good visualization of objects obscured when radiographed in the conventional way by dense overlying structures, or by superimposed shadows of fine structures not in the visualized plane; and second, it permits a precise localization of structures in relationship to external landmarks on the body. Although sectional roentgenography may be applied to a study of any region of the body and views may be obtained such as the lateral dorsal spine with the rib shadows and even a surrounding cast

blurred out, as has been described by Moore (6), the phthisiologist will be most interested in its value for the survey of conditions in the chest. The following uses have been listed by McDougall and Crawford (5) and others: (*1*) analysis of gross disease including tumors in atelectatic areas, the separation of old and new lesions when they are superimposed, and the revelation of bands of tissue through cavities, (*2*) diagnosis of cavities in regions of dense lesions which are not seen on the regular films, (*3*) the localization of cavities and the localization of the component parts of multiple cavities, (*4*) postthoracoplastic analysis especially of cases with positive sputum, and (*5*) the study of artificial pneumothorax such as the zone of collapse in cases without free collapse, the site and nature of adhesions and the differentiation of localized spontaneous pneumothoraces from cavitation. It has also been used in the study of cases of Hodgkin's disease, intrapleural cysts and lung abscess.

Roche (7) feels that owing to the abolition of superimposed shadows, especially of the ribs and clavicles in the upper lung fields, and to the use of the Potter-Bucky diaphragm, sectional roentgenography gives a clearer representation of the lesions and is superior to the use of hard rays in the elucidation of underlying lesions in relatively opaque areas and in the presence of pleural thickening. Although some writers have called attention to the value of serial sectional films in analyzing the pulmonary vessels and the bronchi and their related pathological conditions, Dunham (3) feels that stereoscopic films are superior for this purpose. He joins other authors, however, in the acclaim of sectional roentgenography for studying dense lesions and for postthoracoplasty cases.

At this institution sectional roentgenography has so far found its greatest value in the presurgical mapping of cavities and surrounding areas. Exposures made with a one-half inch separation between planes from the front to the back of the chest give an accurate localization of the extent and position of the cavity and information concerning the presence of air-bearing or fibrous tissue in front or back of the cavity which cannot be obtained in any other way. The preoperative report to the surgeon thus obtained, giving the anteroposterior dimension of the cavity and the distance of the anterior and posterior cavity walls from specified ribs in front and back, is precise information of inestimable value.

In a stereoscopic pair of films, the rays which outline a cavity are tangent to the outermost border and when observed in a stereoscope it

is the plane of maximum sectional width which is seen and which determines the relative position toward the front and back. If the cavity is spherical it may be assumed that the frontal and posterior extent from the localized plane is about equal to its radius as seen in frontal section. However, the cases which come to surgery are usually not round cavities but are more apt to be grossly irregular, cavernous areas surrounded by dense fibrous tissue which distorts the shape. With a stereoscopic pair

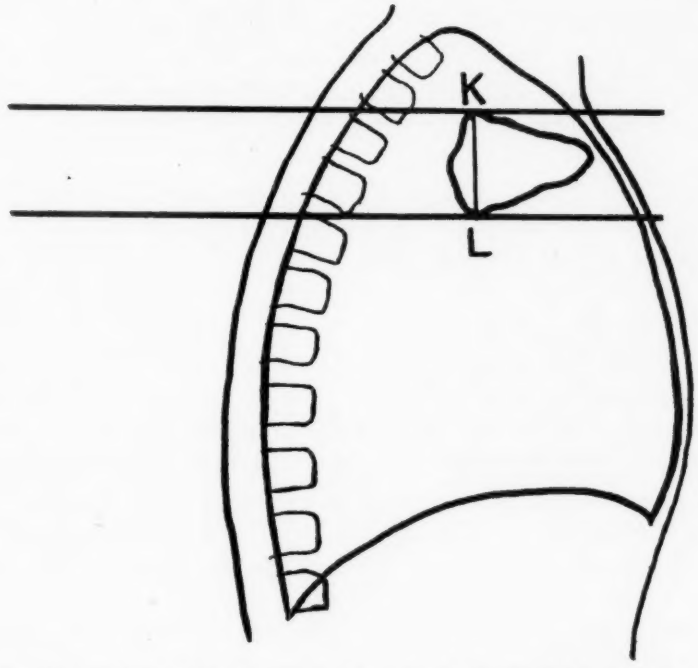


FIG. 4. Diagram showing how dorsoventral stereoscopic films may give a faulty impression of the location of a cavity. The rays from the tube which delineate the cavity are those tangent to the periphery at K and L; when viewed the excavation would appear to be in the midlung and the anterior extension would not be evident.

the rays which define the location of the cavity by being tangent to the outermost periphery can readily give a faulty interpretation of the anteroposterior extent of the area. This is illustrated in figure 4 which represents a lateral section of a cavity such as might be obtained in a surgical case. Dorsoventral films would define the plane KL because it is only at points K and L that the rays are tangent to the border of the cavity. Such a case studied in the stereoscope would localize the

FIG. 5A

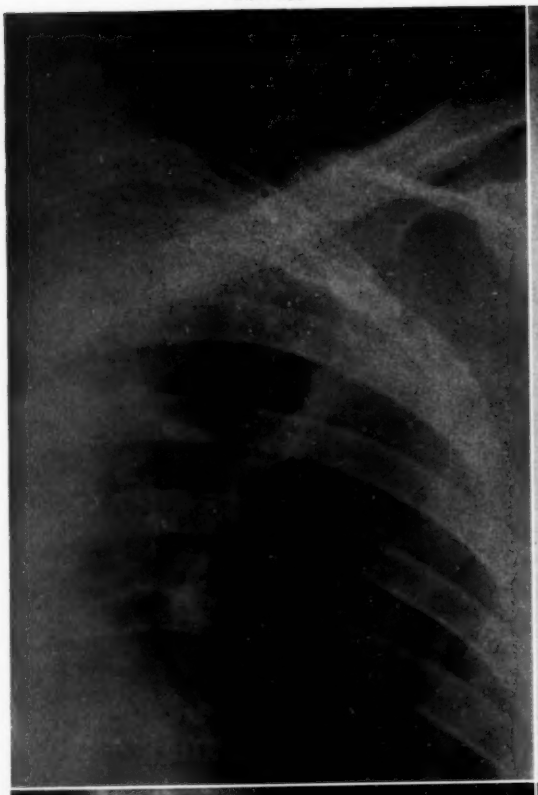
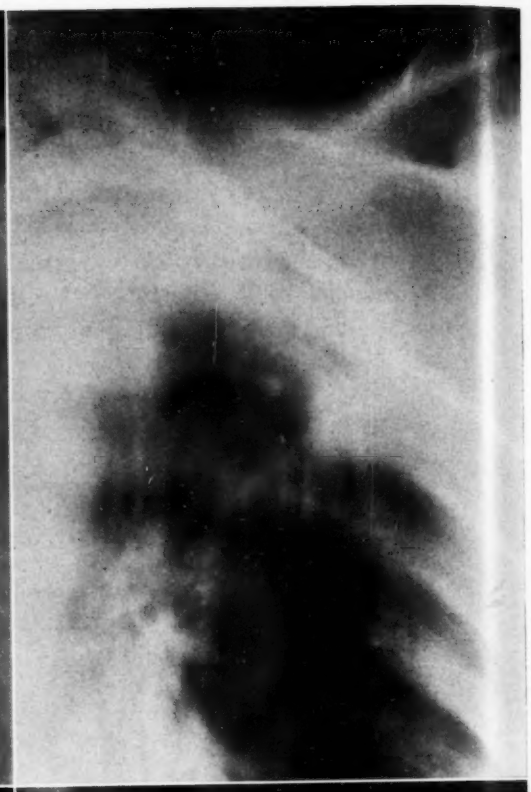


FIG. 5B



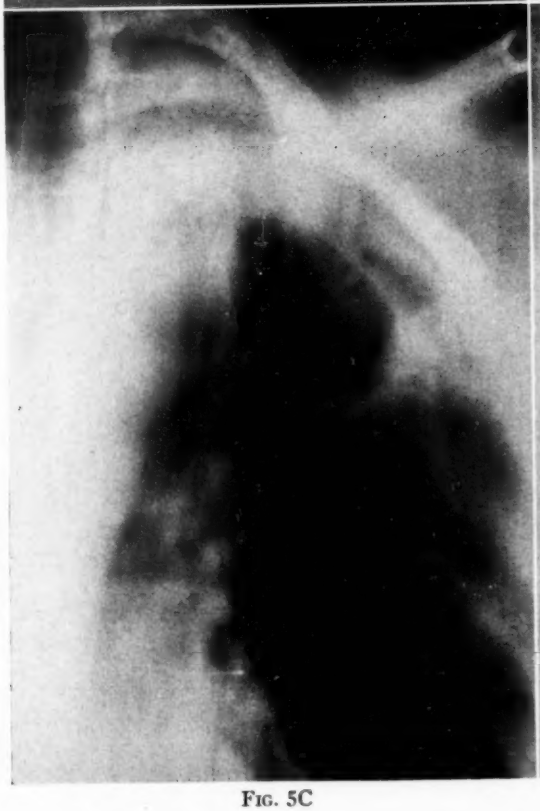


FIG. 5C

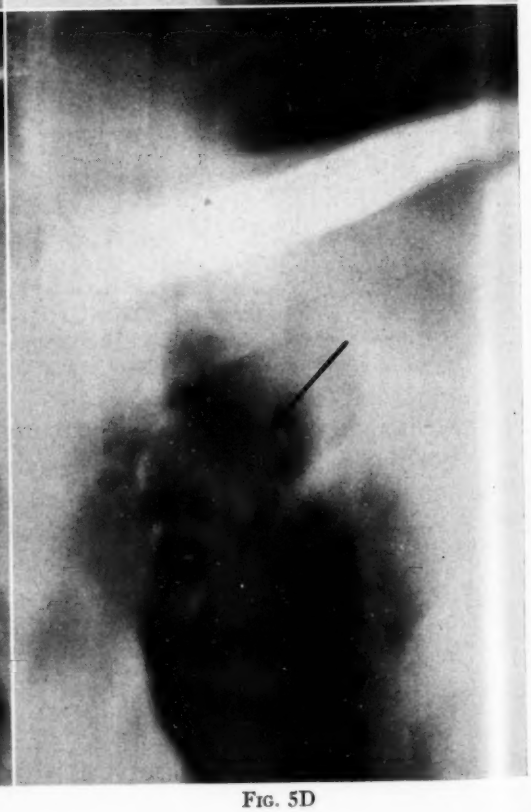


FIG. 5D

cavity as being about midway between the front and back of the chest and would not indicate the forward extension almost to the anterior wall. A lateral exposure would better reveal the true conditions but because such lesions are usually located in the upper lung regions the shoulder shadows prevent a satisfactory view. Serial sectional roentgenograms are ideally fitted for such cases for they map accurately the complete cavernous area.

Serial sectional roentgenograms have also demonstrated in one case (figure 5) the presence of air-containing tissue between the posterior cavity wall and the chest wall as indicated by the blackness of the area and the linear shadows of the vascular tree, whereas they showed the front of the cavity extending nearly to the anterior chest wall and a dense thickened pleura and fibrous tissue lying between the anterior cavity wall and the front of the chest. The surgeon reported that this modified his approach to the case on pleural stripping for extrapleural pneumothorax and that the findings were confirmed at operation.

SUMMARY

The basic principle of sectional roentgenography is briefly outlined.

An inexpensive method, invented by Twining, of attaching the ordinary Bucky diaphragm to the tube column for securing sectional roentgenograms is described and the technique of its use is detailed.

Some of the values to the phthisiologist of study by this method are reviewed and the unique superiority of serial sectional roentgenography in precise preoperative localization and mapping of cavities and surrounding tissues is indicated.

REFERENCES

(1) ALEXANDER, G. H.: A simple and inexpensive tomographic method, Am. J. Roentgenol., 1938, *39*, 956.

(2) ANDREWS, J. R.: Planigraphy, I. Introduction and history, Ibid., 1936, *36*, 575; II. Mathematical analysis of the methods, description of apparatus, and experimental proof, Ibid., 1937, *38*, 145.

FIG. 5A. Conventional radiogram of cavernous area in left upper lung.

FIG. 5B. Sectional roentgenogram of same case at one and one-half inches from the fourth posterior rib shows the blackening and normal lung markings of air-bearing tissue between cavernous area and posterior chest wall.

FIG. 5C. Midsection of same cavity in the plane two and one-half inches anterior to the fourth posterior rib. Note the fibrous tissue at the lower outer border.

FIG. 5D. Section four inches from the posterior chest and almost in contact with the anterior lung margin at the first interspace. Note how dense tissue overlies the upper and outer part of the front face of the cavity.

(3) DUNHAM, K.: Editorial, The value of tomography in the diagnosis of pulmonary lesions, Am. Rev. Tuberc., 1937, *36*, 290.
(4) KIEFFER, JEAN: The laminagraph and its variations, Am. J. Roentgenol., 1938, *39*, 497.
(5) MCDOUGALL, J. B., AND CRAWFORD, J. H.: Tomography, Am. Rev. Tuberc., 1937, *36*, 163.
(6) MOORE, S.: Body section roentgenography with the laminagraph, Am. J. Roentgenol., 1938, *39*, 514.
(7) ROCHE, H.: Control of rest and exercise in pulmonary tuberculosis, Brit. J. Tuberc., 1938, *32*, 89.
(8) TWINING, E. W.: Tomography by means of a simple attachment to the Potter-Bucky couch, Brit. J. Radiol., 1937, *10*, 332.

EXTRAPULMONARY COMPLICATIONS OF PULMONARY TUBERCULOSIS[1]

An Analysis of 1,116 Autopsies

DAVID PERLA AND S. B. BILLER

In analyzing the postmortem findings in 1,116 autopsies on patients dying with pulmonary tuberculosis after the age of fifteen, a number of interesting observations on the frequency and interdependence of concomitant extrapulmonary lesions were made. Though correlative studies of the clinical and pathological findings in patients with pulmonary tuberculosis are numerous in the literature, accurate postmortem studies on so large a series of cases are infrequent. Certain aspects of this subject have been reported by Rubin (1) in detail in correlative clinical studies with postmortem findings in 500 patients.

Statistical correlations in general are treacherous. A great deal depends on the source of the material. We have depended entirely on accurate postmortem studies where the type of lesions, their anatomical character and extent and tuberculous nature could be accurately defined. Correlative incidence of complications would of necessity be considerably higher than clinical experience would suggest. We are dealing with fatalities only and the figures we have cited must be evaluated in this light. For this reason citation of the literature on the incidence of extrapulmonary complications in patients with pulmonary tuberculosis has been omitted.

In the cases analyzed the group of acute miliary tuberculosis does not include those cases in which miliary dissemination was a terminal event, but refers to instances of acute miliary tuberculosis in which the primary lesion was insignificant.

FREQUENCY OF COMBINED LARYNGEAL AND INTESTINAL TUBERCULOSIS

About one-third of our patients showed evidence of laryngeal involvement at autopsy. Slightly more than one-half had intestinal tuberculosis.

[1] From the Laboratory Division, Montefiore Hospital, New York City.

There seems to be a slight decrease in the incidence of intestinal and laryngeal tuberculosis in the past few years in our institution. In the age groups under forty-five, 2 out of 3 had intestinal involvement. In about 40 per cent, neither the larynx nor the intestines were tuberculous.

It is striking that laryngeal tuberculosis in the absence of intestinal tuberculosis was present in only one patient out of sixteen dying with

TABLE 1

Cases analyzed

AGE GROUP	MALE	FEMALE	TOTAL
years			
15–30	197	155	352
31–45	248	123	371
46 and over	302	91	393
	747	369	1,116

TABLE 2

Type of pulmonary disease

AGE GROUP	CAVITARY		FIBROID*		HEALED		ACUTE MILIARY		HAEMATOGENOUS†		TOTAL	
	M	F	M	F	M	F	M	F	M	F	M	F
years												
15–30	180	144	4	1	4	4	3	2	6	4	197	155
31–45	210	102	28	11	3	1	2	2	5	7	248	123
46 and over	36	10	264	75	0	1	0	1	2	4	302	91
Total	426	256	296	87	7	6	5	5	13	15	747	369
Grand total	682		383		13		10		28		1,116	

* Chiefly fibroid, few with small cavities.

† Excluding acute miliary tuberculosis.

advanced tuberculosis (6 per cent). Intestinal tuberculosis without any evidence of laryngeal involvement was seen in one patient out of four with advanced tuberculosis (25 per cent). In 30 per cent of our autopsied cases both the larynx and intestines were involved. Patients without laryngeal or intestinal involvement were usually in the older age groups and were more apt to have fibrotic pulmonary tuberculosis. In young adult patients the larynx and intestines sometimes escaped, but

in these the disease was also limited to the lungs and was frequently pneumonic in type and rapidly fatal.

LARYNGEAL TUBERCULOSIS

When the patient with pulmonary tuberculosis develops tuberculosis of the larynx, the disease is very apt to involve the intestines as well. About 4 out of 5 patients with tuberculosis of lungs and larynx also had intestinal involvement. The laryngeal condition reflected in general the character of the tuberculous disease of the lungs. If extensive ulcerative lesions of the lungs were present, the laryngeal disease was characterized by ulcerative lesions as well.

In the order of frequency, tubercles appear in: (*1*) the neighborhood of the posterior commissure, and the interarytenoid space; (*2*) the anterior surface of the arytenoid bodies and the aryepiglottic folds; (*3*) the vocal cords; (*4*) the ventricular bands; (*5*) the epiglottis (involvement of the epiglottis as a rule represents a late extension of the tuberculous process, though the epiglottis may be involved alone; unilateral involvement of the vocal cords is usual); and (*6*) the sinus of Morgagni. The trachea is frequently ulcerated in the presence of advanced laryngeal tuberculosis. Following the occurrence of tubercles beneath the mucosa, oedema, congestion and cellular infiltration occur and ulceration supersedes. The ulcerations appear worm eaten and small cavitations develop. The process spreads to the cartilage producing perichondritis and necrosis, and fragments of cartilage may be extruded. One or both vocal cords may be destroyed. In advanced cases all parts are involved with marked destruction and distortion. Even the epiglottis may be destroyed leaving a ragged stump. The course is similar to that of the pulmonary lesion. Fibrotic pulmonary lesions are associated with healing tendency in the laryngeal lesion.

INTESTINAL TUBERCULOSIS

In half of the cases in which the larynx escaped involvement, but the intestines presented tuberculous lesions, the disease in the gut was minimal and reflected a terminal dissemination of the tuberculosis to many organs. In the other half of the instances of intestinal tuberculosis, the ulcers were more chronic and showed various stages in development. Isolated ulcers with thickened edges more frequently occurred in elderly patients with fibroid phthisis.

The pathogenesis of tuberculous enteritis is disputed. It is likely that in most instances ingested tuberculous sputum is the source of autoinfection. Stasis favors infection at certain sites, such as the region of the ileocaecal valve and caecum. In turn, it is possible that tuberculous ulcers by liberating fragments containing tubercle bacilli may start new infections in lower segments. Kaufman (2) speaks of fistulous rupture into the bowel of caseous lymph nodes in the ileocaecal region. We have never seen this in our material, though fistulous communication between loops of gut are occasionally seen.

Another possible source for the tubercle bacilli in the gut is through the bile, and secondary intestinal tuberculosis may occur in this way. Probably rupture of pericholangitic tubercles into the bile channels of the liver occurs. Experimentally it has been shown that the intravenous injection of tubercle bacilli is followed in many cases by their rapid appearance in the bile (Calmette, Breton, *et al.*, (3)). One of us has observed that after intraperitoneal inoculation of guinea pigs with tubercle bacilli the microörganisms may appear in the faeces during the first week, and then subsequently for several weeks no bacilli can be recovered until the disease is disseminated (Perla (4)). The evidence indicates that tubercle bacilli introduced forcibly into the tissues of normal animals enter the blood-stream and are eliminated in the faeces through the bile and gut until immunity against the microörganism is established. With the progress of immunization, the bacilli become fixed in the tissues, are no longer capable of permeating intact mucous membranes and do not appear in the faeces. When the infection is widely disseminated, resistance is overcome and elimination of bacilli recurs. The appearance of tubercle bacilli in the bile in humans would therefore indicate a lesion in the liver (Sasano and Medlar (5)), or may occur as a terminal phenomenon in an intact liver.

It is likely that intestinal complications arise, then, (*1*) as a result of autoinfection from ingested sputum or the excretion of bacilli in the bile, or (*2*) as a result of haematogenous spread. Terminally, not infrequently one sees mucosal tubercles. These reflect a general dissemination.

The high incidence of combined intestinal and laryngeal tuberculosis without other extrapulmonary complications, suggests that laryngeal and intestinal tuberculosis may be due to autoinfection by tuberculous sputum. Ulcerations of the trachea are relatively common with advanced laryngeal disease.

In favor of the theory of autoinfection of intestines and larynx by contact with and ingestion of sputum is the fact that these complications are uncommon in children and that they are less common in adult patients with haematogenous pulmonary disease than in patients with cavitary lesions. Laryngeal tuberculosis in association with haematogenous pulmonary disease as determined by postmortem criteria occurred in 25 per cent of our cases, as compared to its association with ulcerative caseous tuberculosis of lungs in 40 per cent.

On the other hand, when one recalls that almost half of the intestinal cases included in the survey reflect terminal disseminations, the haematogenous origin of the intestinal lesions is strengthened. Undoubtedly both routes of infection can occur.

Intestinal tuberculosis, like typhoid fever, is preferably localized to the follicles and Peyer's patches. The favorite sites are, therefore, in the lower ileum and the region of the ileocaecal valve where most of the follicles are situated. The early infection in the follicles or Peyer's patches appears as a nodular elevation the size of a millet seed. The lesion is first gray, later caseous. Softening rapidly occurs, the mucosa ulcerates and a rounded depression appears. It forms a crater with caseous sides and base. Characteristic tubercles are found in the wall, though frequently only a diffuse caseous process is seen. Isolated tubercles appear in the mucosa, submucosa and muscularis. The ulcers coalesce and deepen and extend peripherally and downward. It is striking that as the ulcer progresses its base thickens due to the granulation tissue in the floor and margins. This explains the rarity of perforation of tuberculous ulcers in spite of the frequency of the lesion. Perforation occurred in 4 per cent of the patients with intestinal ulcers. The ulcerations are annular and may by coalescence reach enormous size. Islands of hyperplastic polypoid mucosa may appear between the ulcerations and the gut may markedly thicken. Tubercles may be seen through the serosal surface and the serosal lymphatics are often outlined and distended with caseous material, so that they are clearly visible as radiating lines extending from the region of the ulceration.

The characteristics, then, of older ulcers may be summarized as follows: They lie as a rule at right angles to the axis of the gut, they are annular and may encircle the lumen, the edges are undermined and thickened, tubercles are seen in the thickened floor. Instead of a caseous floor the tissue is grayish and granular and polypoid islands of mucosa

are seen. Cylindrical epithelium may grow over the surface in the process of repair. Tubercles on the serosa may trace the course of the lymphatics radiating from the ulcerations in stellate forms. They are apt to be beady and prominent. Adhesions may occur to adjacent loops but this is uncommon. Involvement of mesenteric nodes is slight.

If ulcers are severe, healing is characterized by cicatrization and tendency to stenosis. The intestine above the narrowed portion is thickened and dilated. The mucosa is papillary near the narrowed area and polyps are common. Occasionally, small ulcers heal, leaving insignificant stellate scars.

Perforation occurs only in acute ulcers which undergo rapid caseation. The opening is sharply defined and, of course, leads to suppurative peritonitis. The appendix is frequently involved in tuberculosis and may perforate.

Haemorrhages may occur from ulcers but are rarely serious. Rarely, neoplasms may develop on the base of an old partly cicatricized tuberculosis. In the past few years the frequency of intestinal tuberculosis has been slightly decreasing. This may be due to improvement in the diet.

We have stated that in one of every 4 patients (28 per cent) (table 3), dying with advanced pulmonary tuberculosis, the intestine and larynx are both involved. However, in patients under thirty with advanced pulmonary tuberculosis 2 out of 5 have both the larynx and intestine involved (39.2 per cent). In most instances no other extrapulmonary organs are grossly involved, and the intestinal, laryngeal and pulmonary disease show similar clinical and pathological features. The degree of involvement of larynx and intestine is similar in 86 per cent, and dissimilar in 14 per cent.

It is not surprising that the individual reacts to the tuberculous infection in a similar manner in the lung, intestine and larynx if these lesions develop concurrently. The ability or inability to delimit the lesion and repair the injury reflects a general state of resistance and is influenced to a lesser degree by local tissue conditions.

In the nonimmune individual penetration of the mucous membranes of the pharynx and intestines by ingested tubercle bacilli can be demonstrated. In experimental epidemiological studies done some years ago, one of us observed that guinea pigs exposed to cage mates with infected skin lesions acquired the disease by licking the ulcerations of their neigh-

bors. In such cases, lesions in the tonsils and cervical lymph nodes occurred before general infection was manifest or intestinal lesions with mesenteric lymph node involvement were apparent (Perla (6)).

It is not excluded that tuberculosis of the intestinal tract and larynx in humans may occur as a result of infection from without by ingestion of sputum. Local abrasions in the small intestines or larynx may permit penetration of tubercle bacilli. If such were the case tuberculous lesions would develop at the site of entry. Freund and Angevin (7) have recently shown that tubercle bacilli, though fixed at the site of entry in the immune animal, will continue to multiply for a longer period of time and

TABLE 3

Incidence of intestinal and laryngeal tuberculosis in pulmonary phthisis—involvement of intestine and larynx

AGE GROUP	ONLY INTESTINE			ONLY LARYNX	BOTH INTESTINE AND LARYNX			NEITHER LARYNX NOR INTESTINE
	S	L	B		S	L	B	
years								
15–30	24	23	57	12	14	15	109	98
31–45	25	17	53	30	28	12	71	135
46 and over	39	16	39	23	22	8	40	206
Total	88	56	149		64	35	220	
Grand total	293 (26%)			65 (6%)	319 (28%)			439 (38%)

S = Small intestine.
L = Large intestine.
B = Both small and large intestine.

in greater numbers than in the normal animal. However, as Willis (8) showed, the tubercle bacilli appear in the regional lymph nodes in the normal animal within an hour or two, whereas they are not found in the nodes of the immune animal for a period of two or three weeks.

In intestinal tuberculosis, complicating pulmonary disease, the mesenteric lymph nodes are involved to only a slight degree. They remain small and may show a few tubercles. Whether the bacilli reach the submucosa and mucosa by way of the blood-stream or from without, they remain localized in the tissues and the tuberculous process is thus limited.

Local conditions favor the growth of tubercle bacilli in some portions of the intestinal tract more than others. Thus tuberculosis of the stomach is almost unknown. We have seen it only in three instances in

this series (0.25 per cent). In one case it occurred at the site of a gastroenterostomy opening; in a second, a caseous lymph node perforated from without; in a third, it was a mucosal ulcer as occurs in many other parts of the gastrointestinal tract. In the duodenum ulceration occurred in one case out of two hundred (0.5 per cent). The usual sites were in the lower half of the jejunum, the ileum and caecum. Tuberculous ulcerations of the oesophagus are extremely rare. In this series only a single patient presented such a lesion (0.1 per cent).

Tuberculous colitis may occur with little or no ileitis. Five per cent had only the colon involved. Extensive colitis in the absence of tuberculous enteritis was twice as frequent without laryngeal involvement. In agreement with Steinbach (9), Schwatt and Steinbach (10) and Rubin (11), we believe the absence of symptoms or X-ray signs may be consistent with the occurrence of ulcerations at autopsy. Less commonly

TABLE 4

The correlation of extensive tuberculous colitis with laryngeal involvement in patients with pulmonary tuberculosis—52 cases (5 per cent)

AGE GROUP	WITH LARYNGEAL TUBERCULOSIS		WITHOUT LARYNGEAL TUBERCULOSIS	
years		*per cent*		*per cent*
15–30	10	19	16	31
31–45	4	8	10	19
46 and over	3	6	9	17
Total	17	33	35	67

are roentgen changes associated with a normal gastrointestinal tract. (See Granet (12).)

RENAL TUBERCULOSIS

Gross caseous tuberculous lesions of the kidney in patients with advanced pulmonary tuberculosis are, in our experience, a relatively infrequent complication. Tubercles are found with great ease, microscopically, in many patients dying of the disease (20 per cent), but gross involvement occurred in only 8 per cent. Bladder ulcerations occurred in 4 per cent of patients. Tuberculous ulcers in the bladder were always associated with renal or prostatic tuberculosis. Tuberculosis of the kidney was as frequently bilateral as unilateral. Caseous lesions involving the pyramids were no more commonly bilateral than advanced cavitary lesions.

Gross renal caseous tuberculosis was twice as frequent in patients with fibrotic pulmonary lesions (10.7 per cent) as in those with cavitary ulcerative lesions in the lungs (5.9 per cent), and was almost three times as common in patients with haematogenous pulmonary disease (29 per cent) as in fibroid phthisis. Approximately every fourth patient with haematogenous pulmonary disease had caseous tuberculosis of the kidney at death.

The initial infection of the kidneys consists of bilaterally distributed minute cortical tubercles, many of which heal spontaneously. Caseous foci generally develop in medullary lesions, involve a pyramid and ulcerate into the calyx. Colaescence of lesions leads to larger ulceration, cavity formation, ureteral involvement and infection of the bladder. Excellent descriptions of the pathology of the disease may be found in standard textbooks.

TABLE 5

Association of tuberculosis of the genital and urinary tracts in patients with chronic pulmonary tuberculosis

TYPE OF PULMONARY DISEASE	NUMBER OF CASES		GENITAL		URINARY (KIDNEY)	
	M	F	M	F	M	F
Cavitary	426	256	61 (14%)	17 (7%)	29 (7%)	13 (5%)
Fibroid	296	87	57 (19%)	11 (12%)	30 (10%)	10 (11%)
Haematogenous	13	15	6 (46%)	4 (26%)	5 (38%)	3 (20%)
Total	735	358	124 (17%)	32 (9%)	64 (9%)	26 (7%)

It should be stressed that renal tuberculosis of the type we are discussing is absent at autopsy in more than 90 per cent of all patients with pulmonary tuberculosis.

The significance of tubercle bacilluria has aroused a storm of controversy. The reliable evidence in the literature indicates that tubercle bacilli may not pass through a normal kidney (Eisendrath (13)). However, certainly, microscopical tubercles may occur and be the focus for the tubercle bacilluria and yet have little clinical significance. It is our opinion that where tubercle bacilli are found in the urine in a catheterized ureteral specimen they arise in a lesion in the urinary tract. It is true that they may, by reflux, be carried up along the catheter in the ureter from a focus in the bladder or they may be carried into the ureter by the catheter passing over a lesion in the bladder. However, it is unlikely that tubercle bacilli pass through a normal glomerulus. Some years

ago, one of us studied the excretion of tubercle bacilli in the urine in tuberculous guinea pigs by inoculating the bladder contents of guinea pigs killed at varying intervals after subcutaneous and intraperitoneal inoculation with bovine and human tubercle bacilli. The guinea pig's kidney is astonishingly resistant to tuberculous infection. Only in the last week just prior to the expected death of the animal did tubercle bacilli appear in the urine (Perla (4)). Grossly, the kidneys appeared normal, but microscopically an occasional tubercle could be seen in animals killed at a time when the general disease was advanced.

Although there are numerous clinical studies demonstrating the presence of tubercle bacilli in the urine of individuals in whom there has been no evidence of renal tuberculosis, it is not improbable that transient bacteraemia has caused minute local lesions of renal glomeruli which have healed or have been overlooked at autopsy.

It is conceivable that in older age groups tubercle bacilluria may occur without specific tuberculous lesions in the kidneys, where the glomeruli are diseased as a result of arteriolosclerosis.

GENITAL TUBERCULOSIS

Tuberculosis of the genital tract is one-half as frequent in the female as in the male. One female patient in twelve (9 per cent) showed involvement of the genital tract. The vagina or cervix, we have seen involved only once (0.3 per cent). The uterus was occasionally the seat of tuberculous endometritis (6 per cent). Tuberculous salpingitis was the most common type of genital tuberculosis in women (7 per cent). Though tuberculosis of the ovary occurred in about half of the cases with genital tuberculosis, extensive involvement of the ovary was rare. Tuberculous peritonitis by extension from the tubes occurred in every fourth patient with tuberculous salpingitis (1.7 per cent). Tuberculosis of the genital tract, we believe, is always haematogenous in origin.

In the male, tuberculosis of the genital tract was at least twice as common as in the female. One male adult in six with pulmonary disease developed genital tuberculosis (17.6 per cent).

From our observations we conclude that the prostate is most prominently involved and is the first site of genital infection; the process spreads rapidly into the glandular tissue filling the glandular lumina with caseous material and destroying the epithelium.

Retrograde extension to seminal vesicles and epididymis then occurs.

The epididymis was practically never involved without the presence of a focus in the prostate. The prostate was involved almost twice as frequently as either the seminal vesicles (9.5 per cent) or epididymis (8.8 per cent). The disease in the epididymis was more often unilateral, in the seminal vesicles it was more often bilateral. The testes are highly resistant to invasion (2 per cent), and extensive epididymitis was often seen with little involvement of the rete testes or the tubules. Genital tuberculosis in the male occurred in 16 per cent of the cases. The urinary tract was concomitantly involved in every third patient with genital tuberculosis (34 per cent). Tuberculosis of the genital tract may therefore occur without urinary tuberculosis and frequently does (66 per cent). It is haematogenous in origin and in turn is a ready source for further

TABLE 6

The incidence of genital tuberculosis in male patients with pulmonary tuberculosis—132 cases (17.6 per cent)

AGE GROUP	PROSTATE	SEMINAL VESICLE	EPIDIDYMIS	TESTIS
years				
15–30	29	22	14	2
31–45	45	26	22	6
46 and over	48	23	30	7
Total genital	122 (92%)	71 (53%)	66 (50%)	15 (11%)
Per cent of all males	16.3	9.5	8.8	2

haematogenous dissemination. Tuberculosis of the kidney in the male is very often associated with genital tuberculosis.

The relative frequency of genital and urinary tuberculosis may be expressed in another way: of all the male patients with pulmonary tuberculosis, 8 per cent developed gross renal tuberculosis, and of these, 70 per cent had involvement of the genital tract. In the females 8 per cent of the patients showed evidence of involvement of the genital tract at autopsy. In 72 per cent of these patients with genital tuberculosis the kidney was not involved. On the other hand, 7 per cent of all the female patients had gross renal tuberculosis but only one-third of these had concomitant genital involvement.

Genital tuberculosis is present in every second male patient with haematogenous pulmonary disease (46 per cent); in every fifth patient

with fibroid phthisis (19 per cent); and in every seventh patient with extensive ulcerative pulmonary tuberculosis (14 per cent).

Genital or urinary tuberculosis occurred in association with intestinal or laryngeal tuberculosis in about 8 per cent of instances.

In general, involvement of larynx and intestine reflects active progressive disease of the lungs, but renal and genital tuberculosis are associated with fibrotic pulmonary lesions or haematogenous pulmonary tuberculosis.

TUBERCULOSIS OF THE CENTRAL NERVOUS SYSTEM

Tuberculous meningitis was considerably more common in the male patient with pulmonary tuberculosis than in the female. It reflects a generalized infection and in the male is frequently secondary to extension of the tuberculous lesion into the rich plexus of veins about the prostate. The relative frequency of meningitis in females (4.7 per cent) and males (6.7 per cent) with pulmonary tuberculosis was similar to the relative frequency of genital tuberculosis in the two sexes.

AMYLOID DISEASE

The presence of amyloid disease was strikingly frequent in our patients with pulmonary tuberculosis (24 per cent). Though wide spread amyloid disease occurred in association with long standing chronic tuberculosis, no direct correlation between the duration of the disease and the incidence of amyloidosis could be made. Those patients in whom extensive extrapulmonary tuberculous disease was present were more prone to develop amyloid disease. In several instances extensive amyloid deposits were present even though the pulmonary lesion had undergone fibrosis and healing. Clinical aspects of amyloid disease in tuberculosis in our patients were considered by Rosenblatt (14).

SUMMARY

Laryngeal involvement occurs in about one-third of all patients suffering from pulmonary tuberculosis.

Tuberculous enteritis complicates pulmonary tuberculosis in more than half the patients examined at autopsy.

Patients with tuberculosis of the larynx generally develop tuberculosis of the intestines.

The individual reacts in a similar manner to tuberculous infection in the lung, intestine and larynx if these lesions develop concurrently.

Tuberculous colitis may occur with little or no enteritis.

The epididymis is practically never involved without the presence of a tuberculous focus in the prostate.

The testes are highly resistant to tuberculous invasion.

Tuberculosis of the genital tract frequently occurs without urinary tuberculosis.

Tuberculosis of the genital tract is a ready source for further haematogenous dissemination.

Gross renal tuberculosis is absent in more than 90 per cent of all cases of pulmonary tuberculosis at autopsy.

The ratio of the frequencies of meningitis of males and females with pulmonary tuberculosis was similar to the ratio of the frequencies of genital tuberculosis in the two sexes.

In general, involvement of the larynx and intestine occurs in active progressive disease of the lungs, but renal and genital tuberculosis are associated with fibrotic pulmonary lesions or haematogenous pulmonary tuberculosis.

Tuberculous patients with extensive extrapulmonary complications are particularly prone to develop amyloid disease.

REFERENCES

(1) Rubin, E. H.: Amer. J. Med. Sc., 1931, *5*, 663.
(2) Kaufman, E.: Lehrbuch der speziellen pathologischen Anatomie, Walter de Gruyter and Co., Berlin, 1922.
(3) Calmette, A., and Guérin, C.: Compt. rend. Acad. d. sc., 1909, *148*, 601; Ann. Inst. Pasteur, 1913, *27*, 162.
(4) Perla, D.: J. Exper. Med., 1927, *45*, 1025.
(5) Sasano, K. T., and Medlar, E. M.: Amer. Rev. Tuberc., 1924, *10*, 392.
(6) Perla, D.: J. Exper. Med., 1927, *45*, 209.
(7) Freund and Angevin: J. Immunol., (in press).
(8) Willis, H. S.: Amer. Rev. Tuberc., 1925, *11*, 427, 439.
(9) Steinbach, M. M.: Ibid., 1930, *21*, 77.
(10) Schwatt, H., and Steinbach, M. M.: Natl. Tuberc. Assn. Tr., 1922, *18*, 233.
(11) Rubin, E. H.: Amer. Rev. Tuberc., 1930, *22*, 184.
(12) Granet, E.: Amer. J. Digest. Dis. & Nutrition, 1935, *2*, 209.
(13) Eisendrath, D. N.: Surg., Gynec. & Obst., 1938, *66*, 67.
(14) Rosenblatt, M. B.: Amer. J. Med. Sc., 1933, *86*, 558.

PROTEINASE AND PEPTIDASE ACTIVITY OF POLYMORPHONUCLEAR LEUCOCYTES, MONOCYTES AND EPITHELIOID CELLS OF INFLAMMATORY EXUDATES[1,2,3]

CHARLES WEISS

As we become absorbed in the intricacies of tuberculosis research, it is well to recall the statement made by MacCallum (1) many years ago: "The lesions produced by the tubercle bacillus are, in their ultimate analysis essentially like those found in any acute or chronic inflammation, but the proliferative changes are so marked and come so quickly as to give a quite foreign air to them."

In tuberculosis, as in other types of inflammation, it is the polymorphonuclear leucocytes which arrive first at the site of infection, to be followed later by the monocytes. The latter phagocytize, and in many instances destroy the tubercle bacilli and become converted into epithelioid cells (2). Opie (3) investigated some of the proteolytic enzymes contained within these phagocytic cells and attempted to demonstrate a relationship between bacteriolysis and proteolysis by inflammatory exudates. Unfortunately the methods available a generation ago were not entirely adequate for this purpose, as shown by the recent researches of Willstätter, Northrop, and Anson and Mirsky (4). The current conception of the proteolytic enzymes, as presented by Bergmann (5), is given in table 1.

The recent literature on enzyme chemistry suggests the hypothesis that enzymes and antibodies have much in common. Hence the possibility exists that substances which act as activators and inhibitors of proteinases and peptidases may exert similar action on antibodies which destroy bacteria. As a basis for future work on the mechanism of lysis of tubercle bacilli in inflammatory exudates, we studied the cathepsin, dipeptidase, and carboxy-polypeptidase of polymorphonuclear leucocytes,

[1] Presented at a session of the Pathological Section at the 34th annual meeting of the National Tuberculosis Association, Los Angeles, California, June 22, 1938.

[2] From the Research Laboratories of the Mount Zion Hospital, San Francisco, California.

[3] Aided by a grant from the Committee on Medical Research of the National Tuberculosis Association.

monocytes, and epithelioid cells. The first of these cellular exudates was prepared by injecting into the pleural cavities of rabbits a mixture of aleuronat and starch. Mineral oil was used for obtaining the monocytic exudates, while phosphatide A3 derived from *Mycobacterium tuberculosis* H37[4] was employed to produce cells of the epithelioid type. Experimental methods and protocols will be found in separate publications (6, 7).

TABLE 1*

Newer classification of proteolytic enzymes

ENZYME		SUBSTRATE		TYPE OF LINKAGE ATTACKED
Proteinases	Pepsin Trypsins Papain Cathepsin	Genuine Proteins	Haemoglobin Casein Edestin Albumins, etc.	Unknown
Polypeptidases	Papain-peptidase	Polypeptides		Intermediate peptide linkage R | —CO—NH·CH·CO—NH—
	Carboxy-polypeptidase	Polypeptides		Peptide linkage adjacent to terminal carboxyl group R | —CO—NH·CH·COOH
	Amino-polypeptidase	Polypeptides		Peptide linkage adjacent to terminal amino group R | NH_2·CH·CO—NH—
Dipeptidase		Dipeptides	Leucylglycine Glycylglycine	Peptide linkage between terminal amino & carboxyl groups R R | | NH_2·CH·CO—NH·CH·COOH

* After Bergmann (5).

SUMMARY OF RESULTS

Each of the three types of cells referred to contains a cathepsin with an optimum at pH 3.0, the curve of activity extending from pH 1.0 to about 5.5. They also have in common a dipeptidase which hydrolyzes d,l-alanyl-glycine at pH 8.0, but lack a carboxypeptidase capable of splitting chloracetyl-l-tyrosine at pH 8.0. The monocytes may, however,

[4] This substance was supplied by the H. K. Mulford Laboratories, Sharpe and Dohme, Glenolden, Pennsylvania.

be differentiated from the myelocytic type of leucocytes, since only the latter can split d,l-alanyl-glycine at pH 5.5 and hydrolyze gelatin and casein at pH 8.0 (table 2). These cellular enzymes exist in an active state and do not require the addition of activators.

Since epithelioid cells are, on the basis of embryological researches, derived from monocytes, it is of interest to note that they also have an enzyme pattern which is similar to the latter, and not the polymorphonuclear leucocytes. This gives chemical support to the morphological studies of Sabin, Doan and Cunningham (8).

TABLE 2

A comparison of proteinase and peptidase activities of polymorphonuclear leucocytes, monocytes, and epithelioid cells of pleural inflammatory exudates of the rabbit

SUBSTRATE	pH	TYPE OF CELL		
		Polymorphonuclear leucocytes	Monocytes	Epithelioid
Haemoglobin	3.0	+	+	+
	5.5	+	+	+
	8.0	−	−	−
Gelatin	3.0	+	+	+
	5.5	+	+	+
	8.0	+	−	−
Casein	3.0	+	+	+
	5.5	+	+	+
	8.0	+	−	−
d,l-alanyl-glycine	5.5	+	−	−
	8.0	+	+	+
Chloracetyl-l-tyrosine	8.0	−	−	−

These data will, it is hoped, make possible the study of the chemical mechanism of some of the phases of tuberculosis, particularly allergy, immunity and caseation. As pointed out by Opie (9), when caseation is beginning, the monocytes have their greatest proteolytic activity. When this process is completed, all proteolytic enzymes have disappeared. In the light of the recent work of Rondoni (10), it is possible that the phosphatide of the tubercle bacillus is an inhibitor of proteinase activity. However, the rôle of the specific soluble substance of the tubercle bacillus

must also be investigated, since, as has been shown by Sabin and coworkers (8), this substance is toxic for polymorphonuclear leucocytes.

The anti-enzyme substances contained in the serous portion of inflammatory exudates should likewise be studied. Opie (9) demonstrated that, whereas normal blood serum inhibits enzymes of both the polymorphonuclear and monocytic variety, the fluid obtained from tuberculous exudates can inhibit only the former and not the latter. Whether or not the dissociation of the enzyme-anti-enzyme complex in tuberculous exudates is due to the development of a pH less than 5.5 remains to be determined (6).

REFERENCES

(1) MacCallum, W. C.: A text book of pathology, W. B. Saunders Co., Philadelphia, 1917, p. 583.
(2) Sabin, F. R.: Tuberculosis and leprosy, in The Mycobacterial Diseases, edited by F. R. Moulton, A.A.A.S., Lancaster, Pa., 1938.
(3) Opie, E. L.: See references in Physiol. Rev., 1922, *2*, 552.
(4) For bibliography see references 6 and 7.
(5) Bergmann, M.: The Harvey Lectures, Williams & Wilkins, Baltimore, 1935–1936, pp. 37–56.
(6) Weiss, C., and Czarnetzky, E. J.: Arch. Path., 1935, *20*, 233.
(7) Weiss, C., Kaplan, A., and Larson, C. E.: J. Biol. Chem., 1938, *125*, 247.
(8) Sabin, F. R., Doan, C. A., and Cunningham, R. S.: Carnegie Institution of Washington, Pub. No. 82, Contributions to embryology, 1925, *14*, 125.
(9) Opie, E. L., and Barker, B. I.: J. Exper. Med., 1908, *10*, 645; 1909, *11*, 686.
(10) Rondoni, P.: Ztschr. f. physiol. Chem., 1932, *207*, 103.

PRIMARY INFECTION IN ADULTS[1,2,3]

Its Clinical and Epidemiological Aspects

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In 1929 we observed that tuberculosis among students and recent graduates of nursing stood out in bold relief when compared with that among girls of the same age in the general community. Therefore, we arranged to make observations in four schools of nursing. In school I, all students were given a three-month service in a thirty-bed tuberculosis department of the hospital. In school II, there was no tuberculosis service but the occasional patient was admitted for diagnosis or special treatment, such as collapse therapy. School III was similar to school II except that the hospital was larger. In school IV, the students of nursing were sent to a sanatorium for the tuberculous for a six-week period. During the same year we arranged to make similar observations among the students in a school of medicine, where the students resided in a sanatorium and worked with the patients for a period of two weeks. As a control group we selected the students of a college of education, who were in approximately the same age period and resided in the same general community as the students of nursing and medicine.

Our procedure in the schools of nursing and medicine consisted of administration of the tuberculin test to all entering students. Those who did not react to the first dose (0.1 mg.) were given a second dose (1 mg.). If no reaction occurred the test was repeated in a similar manner at six-month intervals as long as the students remained negative. Those who reacted to the tuberculin test on admission, or subsequently became reactors, had X-ray films made of their chests at once and annually thereafter. In the beginning it was impossible to procure complete coöperation in all of the schools, particularly with reference to the X-ray films. However, as time passed, these schools became most coöperative and

[1] Presented at a joint session of the Pathological and Clinical Sections at the 34th annual meeting of the National Tuberculosis Association, Los Angeles, California, June 21, 1938.

[2] From the Departments of Preventive Medicine and Internal Medicine, University of Minnesota, and the Lymanhurst Health Center, Minneapolis, Minnesota.

[3] Prepared with the aid of a grant from the research fund of the University of Minnesota.

in the later years of our observation practically every procedure recommended was accepted.

Of all the students examined to date in school I, which required a three-month tuberculosis service until the latter part of our period of observation, 21.3 per cent reacted to tuberculin on entrance and 81.8 per cent on graduation. In school II, which did not have a tuberculosis service, the average percentage of reactors on entrance was 15.8, while on graduation it was 41.2. In school III, 28.4 per cent of the entering students reacted to the test, while 45 per cent reacted on graduation. In school IV, which has a six-week tuberculosis service requirement, 27.2 per cent on entrance and 67.8 per cent on graduation reacted to the test.

In the school of medicine, 37.5 per cent of the students were positive to the tuberculin test on entrance and 72 per cent were positive at the end of the fourth year. In the school of education, the incidence of positive reactors increased from 24.8 per cent on entrance to 28.5 per cent on graduation. Thus, it will be seen that in the schools of nursing which do not have tuberculosis services the infection attack rate is greater than in the school of education. Moreover, in the schools of nursing which do provide tuberculosis services for their students, the infection attack rate is much greater than in schools of nursing which do not have tuberculosis services. In the school of medicine, where a tuberculosis service is provided, the attack rate is very much higher than in the school of education.

We assumed that those students who entered the various schools as tuberculin reactors had primary tuberculosis complexes somewhere in their bodies and they were kept under observation for any subsequent developments. We were particularly interested in what occurs when primary tuberculous infection, that is, the primary tuberculosis complex, first develops in the adult. During the course of this study we have observed 423 student nurses and 134 students of medicine who became reactors to tuberculin while under our observation. Of this entire group of 557 students, only two in nursing and one in medicine developed any immediate symptoms that might have been due to tuberculosis. These three students had erythema nodosum and one of them presented a temperature elevation for a few weeks. Of the remaining 554, not one presented any external manifestation of the disease; in fact, they would not have known of the presence of the primary tuberculosis complexes in their bodies had it not been for the routine and periodic administration

of the tuberculin test. This situation apparently is similar to that so often observed in the past when the tuberculin test was administered to large groups of children and practically none of the reactors had ever been aware of the presence of tuberculosis in their bodies.

Of the 557 students who became reactors while under our observation, 18 from the schools of nursing and 8 from the medical school presented shadows on the X-ray films of the chest which were interpreted as representing the primary foci, all of which in due time partially or completely resolved. We do not consider these 26 students as having any more significant disease than the remaining 531 who developed primary complexes which were in locations or of such size that they could not be detected on X-ray films. The course of the disease was apparently the same as we have so frequently seen in infants and children. Thus, clinically we have not found the primary complex as it develops in the adult to be significant and, therefore, as is also true in children, active treatment has not been found necessary. However, we look upon all of these students as potential cases of reinfection destructive forms of tuberculosis at some subsequent time.

From the epidemiological point of view, the young adult who develops the primary tuberculosis complex and, thus, becomes a tuberculin reactor has had a recent exposure, direct or indirect, to a communicable case of tuberculosis and this source should be sought as in the case of the child who becomes infected. In young adults, because of the larger number of associates, the determination of the source may be more difficult than in the case of the child. In schools of nursing and medicine, however, we have often found those who previously had not reacted to tuberculin who present definite reactions while in contact with tuberculous patients in the hospital or sanatorium or soon thereafter. In our opinion, it makes no difference whether the exposure occurs in a home, a hospital or a sanatorium, the result is the same with reference to the development of the primary tuberculosis complex. From the standpoint of communicating tuberculosis to others, we feel there is little danger because young adults who develop primary complexes rarely cough or have any sputum during the entire course of development. In some cases, tubercle bacilli may be recovered from the gastric contents but apparently this is not very significant as far as the spread of the disease to others is concerned.

Thus, we must conclude that students in contact with tuberculous

patients in hospitals and sanatoria have definitely greater chances of becoming infected with tubercle bacilli than students who do not have such contact in line of duty. The chance of being infected is proportional to the amount of contact. The primary complex as it develops in the body of an adult is a benign disease and apparently is of no more clinical significance than the primary complex which develops in the body of a child. Epidemiologically, primary tuberculosis as it develops in young adults and is manifested by the tuberculin reaction may be used to considerable advantage in locating the source of exposure, but apparently the lesions are not important from the standpoint of communicating tubercle bacilli to others.

THE PATHOLOGY OF PRIMARY TUBERCULOUS INFECTION IN THE ADULT[1,2]

HENRY C. SWEANY

Although Parrot (1) in 1876 first called attention to the course of primary tuberculous infection, there are certain features that are apparently not even yet clearly recognized. Many workers since then, including Küss (2), Ghon (3) and Ranke (4) among others, have established what has appeared to be a clear-cut type of first infection. These observations have been rather loosely translated into clinical concepts and incorporated into tuberculosis literature in such terms as the "childhood type of tuberculosis" or the "first infection type of tuberculosis." While this tendency has been partly justified, there are several notable exceptions which have begun to appear in recent years. This trend has been reflected in the tendency to lay less emphasis on the difference between childhood and adult types of tuberculosis, so far as clinical classifications are concerned. In searching for a cause of this, it seems that the changing infection rate is of great importance. A generation or two ago there were few adult primary lesions to come under observation, because most people were infected in infancy or childhood.

As a result of the decline of tuberculous infections, however, there are more first infections appearing in adults, and thus the line of demarcation between the childhood and adult types is being obliterated.

It seems opportune, therefore, to attempt a review of our knowledge of this subject with emphasis on the pathological basis for the various differences. It may be well to call attention to features that are not ordinarily appreciated with regard to primary infections in general and adult primary infections in particular.

First, with regard to the primary infection in children, there has been much said about the slight or moderately benign infection but little

[1] Presented at a joint medical session of the Pathological and Clinical Sections at the 34th annual meeting of the National Tuberculosis Association, Los Angeles, California, June 21, 1938.

[2] From the Research Laboratories of the City of Chicago Municipal Tuberculosis Sanitarium, Chicago, Illinois.

about the overwhelming infection with its acute pneumonic disease, ulceration and speedy death. In these latter infections death may occur when the lymph nodes are only in their early evolution, before they have attained their maximum possible size. This type is perhaps what Birch-Hirschfeld (5), Abrikosoff (6) and Schmorl (7) have considered as primary tuberculous bronchitis even to the disregard of the primary law. Although the majority of infections in children are of the clinically insignificant or benign type of acute infiltration with calcified residues developing later in the form of "Ghon foci," the overwhelming type just alluded to must be recognized and, as we shall see, it appears to have a counterpart in adult primary infections.

In previous studies (8) (9) of the pathology of first infections, it was shown, among other things, that there was a tendency for first infections in adults to become confined more to the parenchyma of the lung with a gradually diminishing size of the lymph node component. There was also a tendency for the adult lesions to localize more in the upper parts of the lung simulating the usual reinfection types. Furthermore, they seem much more prone to soften and ulcerate than the lesions of childhood. As a corollary of this, there seems to be less tendency for the lesions to calcify and, when calcification appears, it resembles the lesions of reinfection.

In preparing this report a review of over 800 autopsies of tuberculous cases was made, and the age characteristics of the lesions of more than 300 of them corresponded to infections after fifteen years of age. Of this number about 100 were so recent that there was no question of their being adult infections. Owing to the fact, however, that the age determination, according to morphology alone, is not sharp, and that definite percentages could not be determined, it was thought advisable to arrange the material in groups and select representative cases for each group, rather than attempt to establish percentage ratios at this time.

At the outset, let it be understood that the lesions described are the oldest found in the body. Some may not be the first, but they are all apparently primary so far as we are able to determine.

The largest and most important group of adults is composed of cases that resemble the primary infection in childhood. I should say that about half are of this type. They are young adults who still produce a typical primary complex, as in children. Most of them have lymph node components smaller than in children, but it is only a relative decrease

over those found in childhood. There may be single or multiple parenchymal foci, but only moderate or small lymph node foci with little or no demonstrable systemic generalization. Nearly all cases that have come to autopsy have had ulceration around the parenchymal primary focus.[3] The first case is an ulceration of the lymph node component.

Case 1: M. I. (A866) was a 16 year old boy exposed to his father from December, 1934 to April, 1935. He had a "pneumonia" in June, 1935 and died January 30, 1936 at the age of 18.2 years. The disease process was, therefore, of about two years' duration. There was found a small primary lesion in the right base spreading along the bronchi as well as through the diaphragm. The latter produced a slight peritonitis. The former ascended in the lymph nodes and produced small lesions of 2 to 5 mm. in the lymph node chain up to the hilum and to the paratracheal nodes. One paratracheal node on the left ruptured through the pleura into the left upper lobe, resulting in a tuberculous bronchopneumonia, seven months after infection and seven months before death. The rupture of the node may have been due to acquisition of allergy by the cells of the capsule. The age formula is one characteristic of a tubercle one and a half to two years old. This is a classical small primary lesion in a young adult, of recent origin. The rupture into the lung, however, is unusual, but some such episode is prone to develop in fatal adult primary lesions. All of the lesions seemed prone to develop focal softening in the capsules.

Case 2: L. S. (A544) was a 28.7 year old nurse on whom a diagnosis of tuberculosis was made five years before her death. The X-ray films revealed a primary lesion a year or two before that. She was married at 19 and the infection must have occurred about that time. It consisted of a definite parenchymal lesion in the right midfield and at the hilum. The age of the lesion was determined pathologically as a seven-year type. The first clinical disease, as shown on X-ray, seemed to emanate from the region of the parenchymal primary, and spread on to death. There was a tendency for the tubercles to caseate the capsules and produce tissue "overflows."

Case 3: G. C. (A873) was a 29.5 year old woman at the time of death. There was a soft lesion at the hilum in direct relation to a large contracted cavity in the right upper lobe. The whole process was only three to four years old and perhaps occurred after her marriage in 1925. The process was rather

[3] In my studies on the age factors of primary tubercles, various changes of the components of the tubercle have been recorded as numerical quantities. The totals of each case taken together have been arbitrarily spoken of as a "formula."

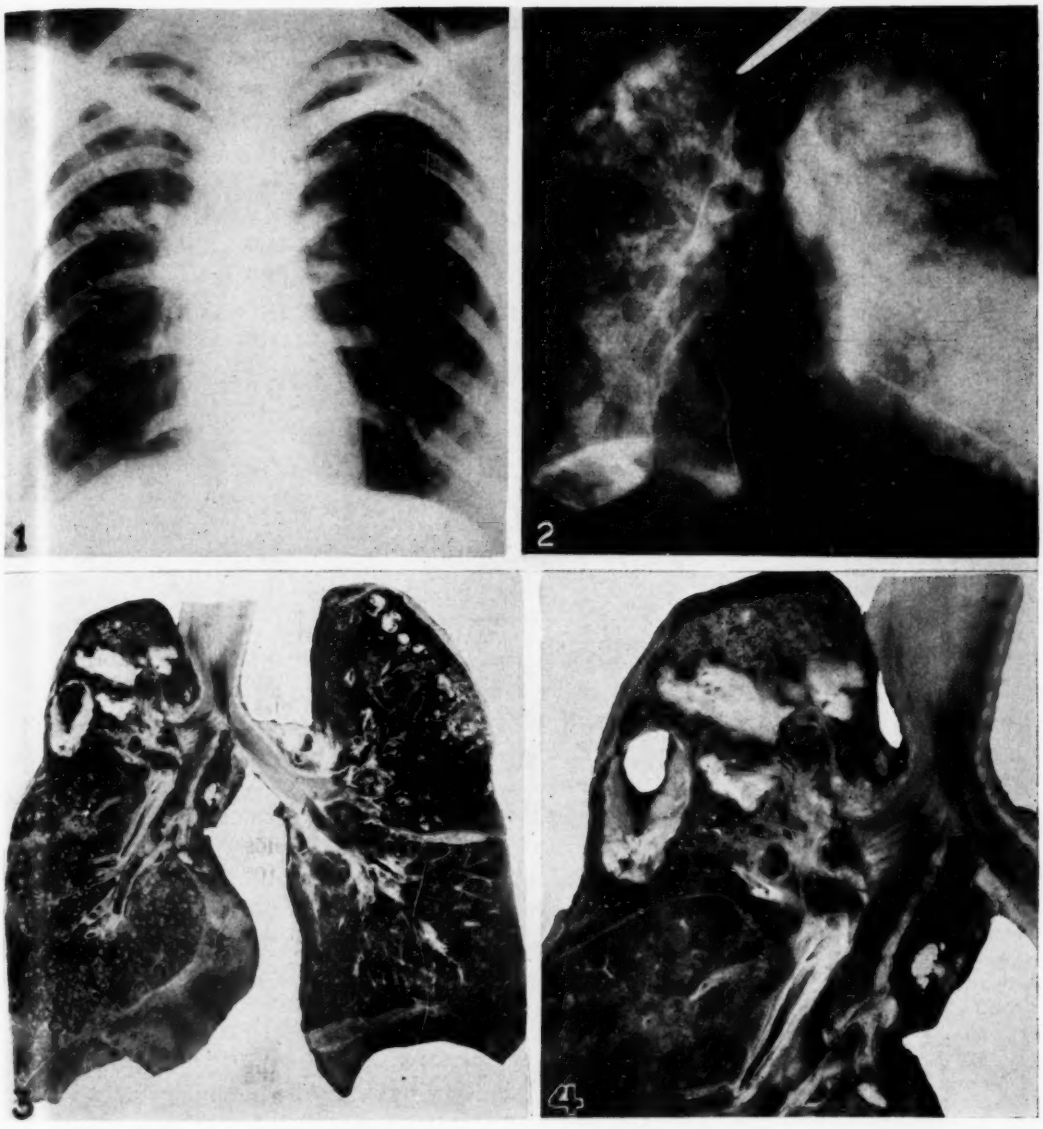

PLATE 1

FIG. 1. Antemortem roentgenogram of case 3. Note large cavity in the right upper lobe.

FIG. 2. Postmortem roentgenogram many months later. Note that there are no calcifications visible.

FIG. 3. Sagittal section of lung through the trachea and bronchi. Note the cavity and infiltrates in the right upper lobe; the Simon foci in the left upper lobe; the acinonodose tubercles in the right base; and the dry caseous primary tubercle in the hilum node.

FIG. 4. An enlargement of the right upper lobe and hilum.

extensive in the right upper lobe and ulcerated early. The lymph node complex was small in comparison. (Plate 1.)

Case 4: J. M. (A358) was a 26.2 year old nurse. She had a rather soft calcified lesion in the right upper lobe with a moderate sized lymph node component at the hilum. The whole process seemed to be of no more than six or seven years' duration. The local parenchymal lesion had apparently overflowed and produced clinical disease which appeared before she completed her nurse's training. The features are characteristic of an adult primary that ulcerated around a multiple primary lesion in the parenchyma.

Case 5: E. O. (A509) was a 34 year old housewife who had numerous soft caseous and dry calcified nodular lesions throughout both upper lobes with definite moderate sized lymph node components at the hilum. The whole process was not over seven years old and seemed to have spread gradually throughout the parenchyma causing, at first, caseous tubercles to be followed by ulcers, then gastrointestinal tuberculosis, and finally a generalization and death.

Case 6: S. C., a 42 year old physician, working in a tuberculosis sanatorium, contracted what was thought to be a mild pneumonia in 1927. It ran an uneventful course, with recovery. An X-ray picture taken in 1930 revealed a rather soft type of calcification in the region of this old pneumonic process. This calcification contracted to about half its size by 1935 and still more by 1938. A definite bronchopulmonary lymph node component had become visible by 1935 and was about one-half the diameter of the parenchymal lesion. It seems to be rather definite that the pneumonia and this lesion occurred near the same time and perhaps represent one and the same process. It shows the tendency of the parenchymal lesion to develop more than the lymph node lesion in adults. In this instance the local lesion has not shown an extension to date. (Plate 2, figures 1 and 2.)

As the age level rises, or as other unknown factors enter, the lymph node component may be still smaller and there may be a tendency for the lesions to become more ulcerative and localize in the upper parts of the lungs.

Case 7: P. S. (case number 45063) is a 27 year old female who had been nursing for four years in a tuberculosis sanatorium. An X-ray picture taken in 1935 revealed little or nothing in the chest, but in 1936 a lesion of about 2 mm. appeared in the right upper lobe. There was also a small lymph node involvement toward the hilum. In 1936 there was an infiltration appearing

in the parenchyma which became ulcerated into a small cavity by 1937. It would seem that the ulceration emanated from the region of one of these small calcifications. This case is one where the oldest lesion in the body, as

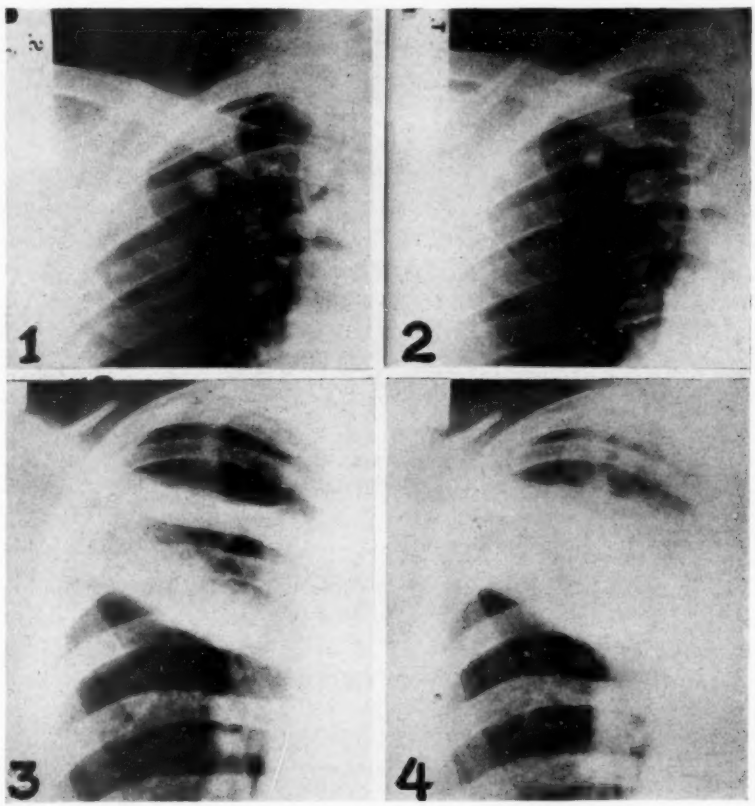

PLATE 2

FIG. 1. Roentgenogram of case 6 taken in 1930. Note large calcified infiltrate in the right upper lobe.

FIG. 2. The same, in 1938. It is about half the volume. There is a small lymph node calcification out from the right hilum.

FIG. 3. X-ray taken of case 19 on admission to the Sanitarium, with a completely negative tuberculin.

FIG. 4. Same, two months later—tuberculin positive. There is no evidence of a smaller "herald" focus.

determined by X-ray, appeared in the right upper lobe and gradually ulcerated in spite of rest and a gain of twenty pounds in weight. The sputum became positive and as a result pneumothorax was instituted. It is a fair presumption that this is an adult primary process spreading to active disease.

Case 8: This case was furnished through the courtesy of Dr. R. H. Stiehm (patient A. G., no. 79975). Definite contact was elicited, but a negative tuberculin was found before clinical disease began and after the contact. The tuberculin reaction was negative in September, 1934. There was exposure in a rooming house from October, 1934 to March, 1935 and the tuberculin reaction became positive by March, 1935. There is little to be seen in the X-ray film in March, 1936, but in May, two months later, there are a few tiny lesions in the right upper midfield and subapical region. The disease progressed until March, 1937 when there are infiltrations seen around the small calcifications in the right upper lobe with definite small ulcerations and a recent (Assmann) infiltrate undergoing ulceration in the apex of the left lower lobe. This raises the question if many other such infiltrates may not arise in a similar manner. The exacerbation may also be far away from the primary and may be either bronchogenic or less commonly blood borne.

Case 9: S. K. (A652) a 28.7 year old woman who was exposed to her sister about six years before her own death. There were small lesions in the right upper and bronchopulmonary nodes quite similar to those observed in the two preceding cases. The oldest cavity was adjacent to the small parenchymal calcification. There was a progressive disease to death. No other calcifications were found in the body, as revealed on X-ray films. The pathological age was that of a six year lesion. The presumption is that this was an adult primary lesion dating from her exposure to her sister, forming one or more infiltrates (Assmann), ulcerating around one lesion and progressing on to death. This case was similar in every detail to the two preceding cases, both of which are still living. (Plate 3.)

This tendency to parenchymal localization may become so exaggerated that only a bronchopulmonary node component may be present and there may be even nothing left but a local calcified residue with a total disappearance of the lymphatic components if they ever were present.

Case 10: B. L. (A309), a 26.4 year old school teacher of Scandinavian descent, came to Chicago from Minnesota three years before her death. She developed a cough in August, 1928 and died in November of the same year. A postmortem X-ray film of the lungs revealed several small calcifications in the left upper lobe and a very small one in the bronchopulmonary nodes toward the hilum. These averaged about 2 mm. in diameter and they were situated around the oldest cavities. These cavities seemed to result from ulceration of soft infiltrates about 2 cm. in diameter. There was a terminal spread to the right upper lobe in the form of a tuberculous pneumonia. The age of these calcifications is not over three years and possibly around two.

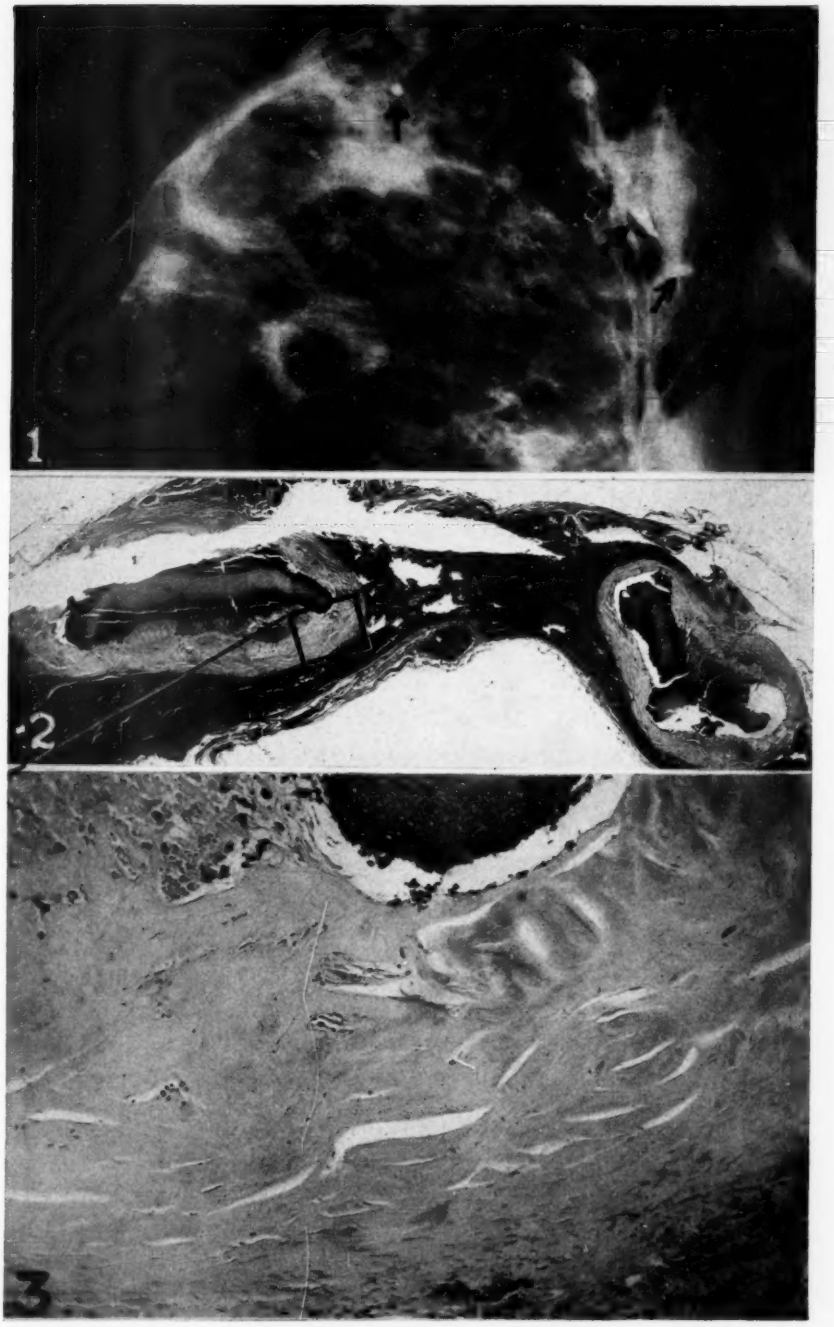

PLATE 3

FIG. 1. Postmortem roentgenogram of right upper lobe of case 9. Note small calcification outside the cavity and the small calcifications to the right of the trachea. The first antemortem X-ray film revealed only an excavating infiltrate. Perhaps the calcification is only a later satellite focus.

FIG. 2. Low power magnification of the latter. × 8

FIG. 3. A higher magnification. This is a six to eight year process. × 100

The presumption is that she acquired her tuberculosis after coming to Chicago, which was three years before her death. The spread caused larger and larger infiltrates, until several of them developed into cavities. There are many cases of this type. (Plate 4.)

Case 11: E. B. (A574) was a 28.2 year old female at the time of death who was exposed to her sister about eight years before her own death. She was of Finnish descent. At postmortem there were found only two calcifications in her body by X-ray study. These were around a small cavity in the right upper lobe and were characteristic of a primary tuberculous lesion of about eight years' duration. The presumption here seems to be very strong that her first infection occurred in the region of these primary calcifications where the oldest cavity appeared, and spread throughout the rest of her lung, ultimately ending in death.

Perhaps the most interesting, yet the least understood and almost unrecognized type, however, is the overwhelming primary infection of adults where the whole process is waged in the parenchyma as a pneumonic or ulcerative process just as described for children. Many of these cases have no resemblance to primary lesions and few have even a remnant of a primary complex. They are justifiably considered by clinicians as reinfection types, because there is not a shred of evidence to the contrary until all the facts are assembled after a postmortem examination and when tuberculin studies before death and meticulous pathological studies after death are compared.

These cases may be divided into two groups, the rapidly fatal and those that recover at least temporarily. The first type has been shown in a former report (8) and is illustrated by the following cases, ranging from those in which vestiges of a primary complex are still present, to rapidly fatal overwhelming infections without any detectable primary.

Case 12: C. K. (A390) was a 24 year old woman exposed to a tuberculous sister about 2.5 years before death. It is possible that both sisters obtained the infection from a common source about six months before that time. At any rate, the infection time had been placed at three years, and the lesions are compatible with this age. There were small subpleural, probably primary lesions in the subapical region with gradually expanding lesions to large excavated infiltrates 2 to 3 cm. beneath the pleura. There were small lymph node tubercles toward the hilum. There was a spread to the opposite upper lobe with recent ulceration to both bases and extensive spread to the intes-

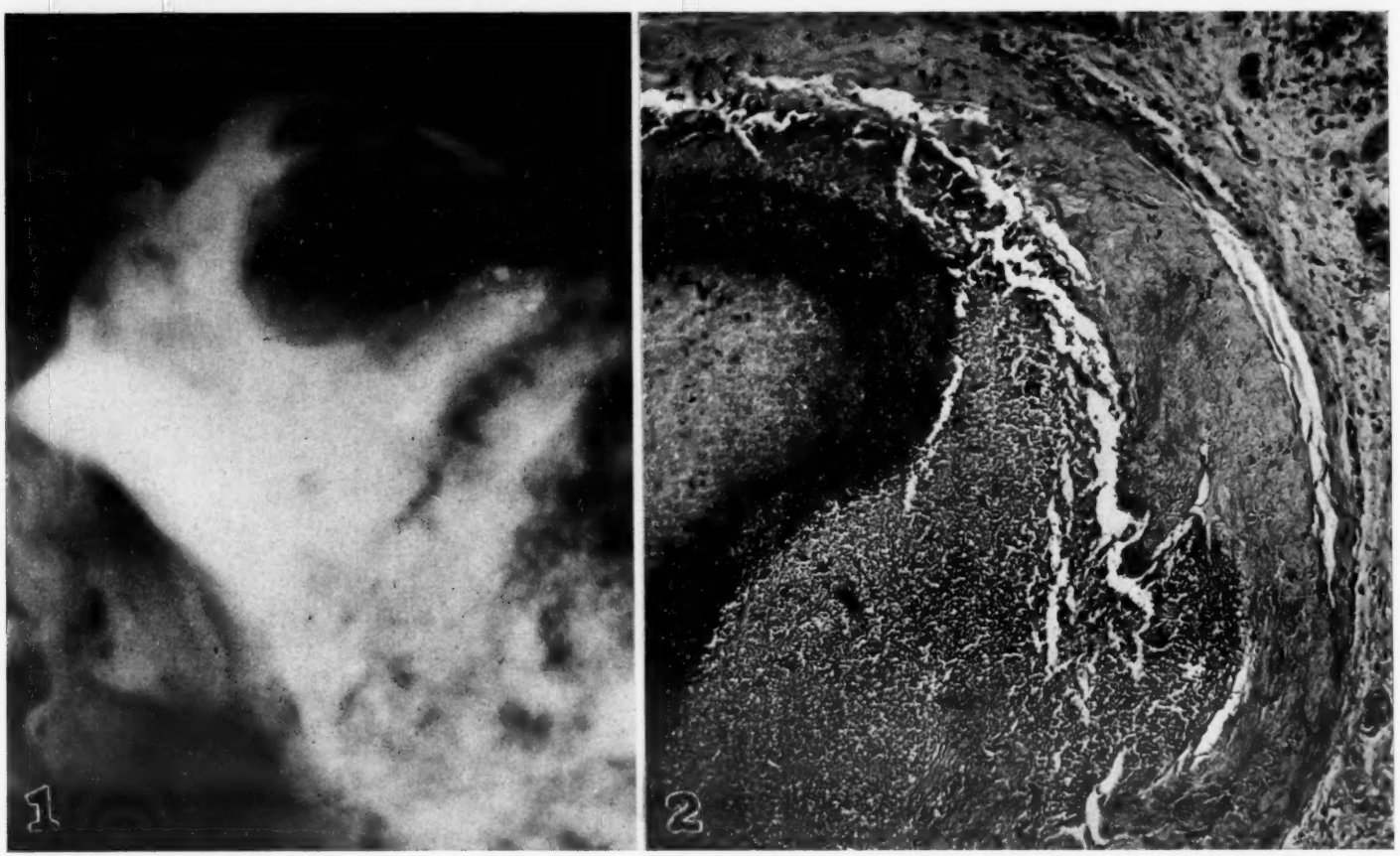

PLATE 4

FIG. 1. Postmortem roentgenogram of left upper lobe of case 10. Note the small calcifications around the cavity and a small lymph node calcification in a bronchopulmonary node.

FIG. 2. A photomicrograph of part of one of the small calcifications. Note early calcification and "specific capsule." This is a two year process. × 130

tines. The presumption is that this is a first infection in a young adult with an abortive primary complex. (Plate 5.)

Case 13: D. K. (A415) was a girl dying at the age of 17.8 years. Her father visited his brother, a war veteran, who had tuberculosis. After coming home the father developed a protracted cough that was later found to be tuberculosis. Subsequently, his daughter (this patient) began to cough, and she was found to have tuberculosis as well as her twin sister. Still later her brother was found to have acquired the disease. The age of the infection was thought to be about five years, but the age formula of the tubercles sectioned was only of a three year type. There were a few soft calcifications beneath the pleura and along the left subapical bronchus, in the left base, left tracheobronchial lymph nodes and the right bronchopulmonary lymph nodes. There was the usual progressive terminal disease. This case is similar to the preceding.

Case 14: Z. C. (A392) was an 18 year old girl who was exposed to her father, an open case of tuberculosis. Her sister was also infected about the same time. She had an appendectomy as the first possible sign of tuberculosis, at 15 years of age, and was never well afterwards. Four months later "whooping cough" developed. Six months later she had "influenza" with an abscess of the middle ear. One year later she had another attack of "influenza." Clinical tuberculosis began four months later with chills, fever, pleurisy, etc. She died nine months later at the age of 18 years and one month. She was infected, therefore, some time between three and four years before her death. The formula was about a two year type, but the process was so exudative and ulcerative that this was not reliable. There was found a progressive ulcerative process in the left base with a cavity in the lingula. There were several nodular tubercles around the periphery. No definite lymph node complex was found. There was a more recent spread to both upper lobes and an extensive spread to the intestines.

PLATE 5

FIG. 1. Antemortem roentgenogram of case 12.

FIG. 2. Postmortem roentgenogram of same. There are no calcifications visible.

FIG. 3. Strip showing age at infection (21); earliest symptoms (21.2); diagnosis of disease (23); admission (23.9); and death (23.9).

FIG. 4. Subpleural dry infiltrates from left upper lobe. Note older lesions near the pleura and large infiltrates toward the hilum, by direct extension. × 6

FIG. 5. Bronchopulmonary lymph node complex. Note the size of pulmonary artery. × 6

FIG. 6. Another lymph node complex nearer the hilum, shown by the larger size of the pulmonary artery. × 6

FIG. 7. Higher magnification of subpleural area of fig. 1. × 90

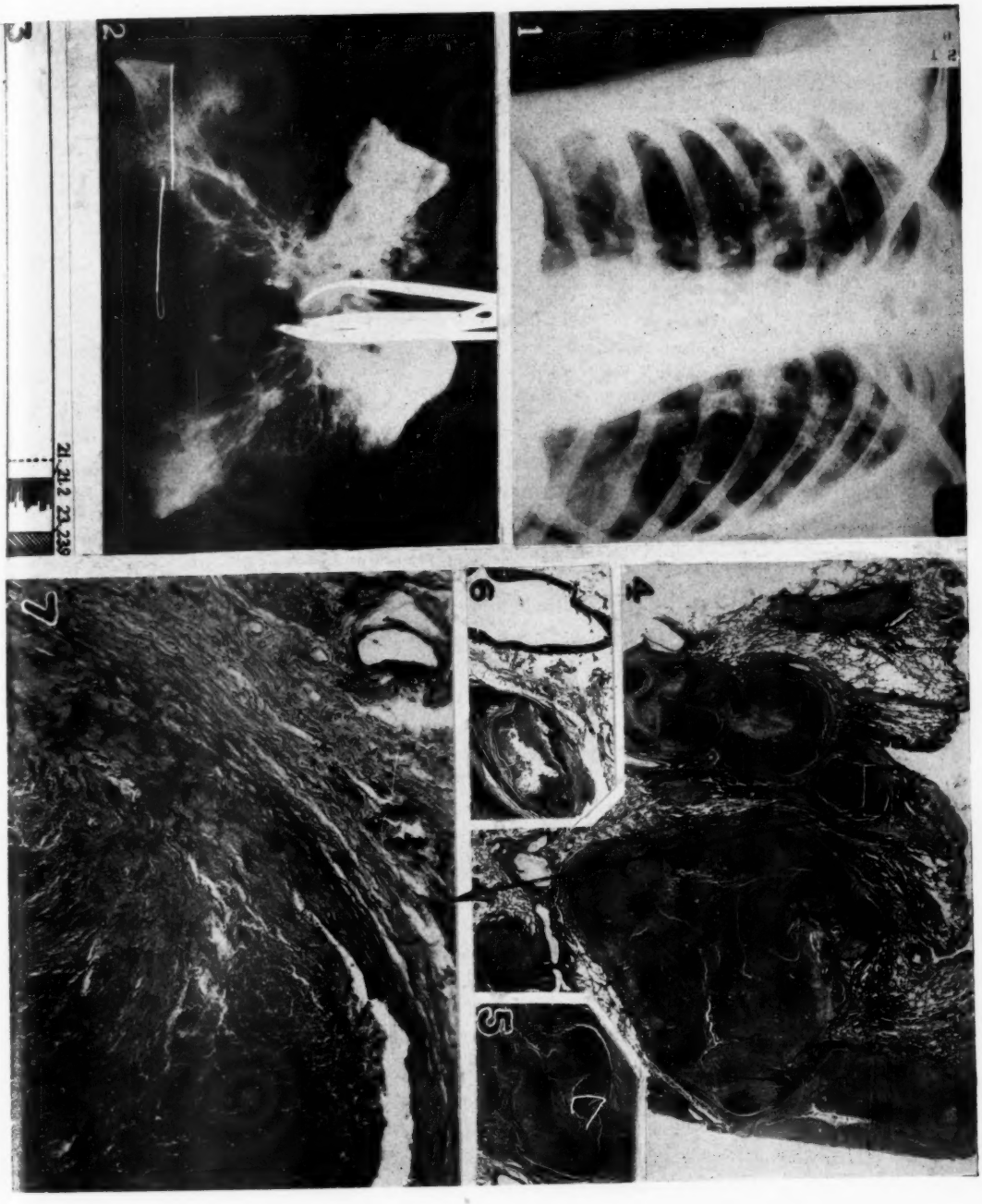

PLATE 5

Case 15: E. J. (A752) was exposed to a tuberculous sister seven years before his death. He was ill four years. There was a complete excavation of the left lung and a spread to the right. There was a lymph node component at the left hilum of a three year type. This was thought to be a massive primary, ulcerating the whole left lung before calcifications could form and producing only a lymph node component, in direct relation to the process in the left lung.

Case 16: G. S. (A424) was a girl 18.2 years old at death. She developed the first symptoms in March and died in October, 1930. Although there was no history of contact this whole process seemed to be an overwhelming primary infection. It was acquired about January, 1930. There were no calcifications anywhere and the tubercles were all of a very recent age. There were no caseous lesions in the hilar lymph node. Because of the fact that this girl was raised on a farm in Wisconsin, had no history of contact and came to Chicago only three years before her death, the presumption is that she acquired an overwhelming primary infection that ran a very rapid course without producing any definite signs of a classical primary lesion.

The group that temporarily recovers is interesting in that the disease appears to begin with all the violence of a fatal case except the subjective symptoms are not so marked and the patient temporarily or completely recovers. This may be analogous to Ornstein's (10) clinical grouping of "benign acute tuberculosis."

Case 17: J. L. (A639). This case was reported before (11), but it is repeated here because it seems to represent a definite type, namely, the lobar pneumonic involvement of tuberculosis, leaving behind many calcifications of recent age but, nevertheless, the oldest found in the body. There was a fair presumption that the lobar pneumonia was a primary type of tuberculous infection in an adult. Most of it became resorbed, but many small foci formed calcifications and the large central mass ulcerated. Following two successive pregnancies she developed disseminated tuberculosis. The lesions were of a four year type corresponding to the pneumonia.

Case 18: A. M. (A658) was a 23 year old woman at death. She was exposed to her husband from four years to two and a quarter years before her own death. The age formula is compatible. Her clinical disease began two years before her death. There were four soft calcifications in the right base and a larger one in a bronchopulmonary node toward the hilum. There was an extensive fibroulcerative tuberculosis on the right side with spontaneous pneumothorax and a bronchopleural fistula; a moderate involvement in the left upper lobe and extensive enteritis and marked fatty changes in the liver.

Case 19: W. K. (case no. 42192) was a 26 year old man entering the Sanatorium with a definite diffuse cloudy consolidation in the right upper lobe. Tuberculosis was suspected. The tuberculin test was negative on admission but was strongly positive two months later. It seems rather definite that this is the benign type of lobar involvement leading to lobitis (Bernard (12)) and is similar to the preceding cases except for the localization. The negative tuberculin reaction seems to prove that this is a primary infection in a man 26 years old. (Plate 2, figures 3 and 4.)

As mentioned before, the rapidly progressive types may occur also in children, but usually not without lymph node residues. This whole group will be discussed later and may be related to size of dosage or to a peculiar virulence of the microörganisms.

Finally, there is another type of which I have seen only a few cases in adult white people, although it is found not infrequently in adult Negroes and commonly in infants and children. The lesions in this type resemble grossly the huge masses found in some forms of silico-tuberculosis. This form appears to be related to some peculiar attenuation of virulence of the parasite and results in a slowly progressive lymph node disease.

Case 20: B. M. (A1010) was a 30 year old woman whose disease began seven years before death. There is no history of contact, but the oldest lesions seemed to show about an eight year process. It was perhaps two or three years older. From these oldest lesions there was a continuous overflow into the lymphatics producing varying ages of hyperplastic lymph node tuberculosis in the hilum region.

Case 21: E. W. (A879) was a 21 year old woman with no history of tuberculosis contact. Her clinical disease was three years and the pathological appearance of the lesion was about six years, although it may have been one or two years older. At any rate there was a local pulmonary lesion that had developed into a large cavity and a massive lymph node involvement at the hilum. This is like the preceding case, an "overflowing" hyperplastic lymph node involvement in a young adult.

Case 22: M. J. (383) was a 43.1 year old woman born and raised in Minnesota who had spent about half of her life in large cities. She took ill with bronchitis in November, 1928 and died in January, 1930. There was apparently a primary infection in the right base that spread up the lymphatic system producing huge masses of lymph node tuberculosis around the hilum. There was a terminal peritonitis and pleurisy with effusion and numerous gram-positive non-acid-fast bacilli in the peritoneal fluid. Only a few acid-fast bacilli were ever found, but animals and cultures were positive for tubercle

bacilli. The presumption in this case is that there was probably a primary tuberculosis caused by an atypical tubercle bacillus. Although no older tuberculous process was found, a small earlier lesion may have been present and completely disappeared.

DISCUSSION

The differences in the types reported above are so divergent from the classical types in childhood that the subject was thought to be worthy of a special report in order to appreciate better the changes that may appear as a result of the increase in adult primary infection. In many of the cases reported there may be a question raised as to their primary character. Naturally it cannot be denied that every one may have been infected before, and the infections were entirely resorbed or were too small to leave a caseous or calcified residue. In two cases it would be necessary to assume that the tuberculin test also became negative after such healing. The probabilities are, however, that they were truly primary or "essentially" primary lesions. The strongest reasons for this assumption, besides their being apparently the oldest lesions, were that the infection rate is so low in Chicago to-day that more than two-thirds of the population is uninfected at the time of high school graduation.

Assuming that they are first infections, let us inquire into the cause of the difference between these and childhood types.

First, and very important, is the difference in the anatomical basis, of which there are many factors, but most important is perhaps the anatomy of the lymphatic system. From a rather sparsely scattered but potentially active lymphoid tissue in infancy there is an increase to midlife, and then a diminution, due to atrophy, in old age. The effect of this seems to be a tendency to localize the infection in adult life rather than allow it to generalize throughout the body. In middle life the rich lymphatics seem to be partially responsible for the effect by localizing the infection, while in old age the lymphoid tissue is destroyed, atrophied or blocked so that there is probably a similar effect but for a different reason. This difference was pointed out by Krause (13) many years ago, who compared the child to the guinea pig and the adult to the rabbit in their response to infection.

The principal variation, however, between the young and old, so far as tuberculous disease is concerned, is no doubt the difference in speed of growth of the body cells. It is possible that the fibrous tissue forms so slowly in the adult that it gives the parasites an opportunity to outgrow

it and thus lead to the overflowing type of tubercle or to the actual rupture of tubercles into the surrounding lung tissue. Some cases of adult primary infections seem to spread in this manner, and other features, especially the particularity of lymphoid anatomy, favor spread. First the parasites "overflow" into the surrounding alveoli, then they become free in bronchioles whence they spread to nearby lobules or by the larger bronchi to more distant regions. These types may be in many respects like the fine and coarse dissemination of Loeschcke (14). As to the understanding of the phenomenon of capsule formation, there seems to be a parallel in the work of DuNoüy (15) on the healing of wounds. He found that wounds heal more slowly as people get older and that chicken heart cells, cultured by Carrel's method, grow more slowly as they are subjected to chicken serum from chickens of increasing ages. These facts seemed to have an application to tubercle formation. In a series of adult primary lesions, previously reported, in which the time of infection was rather definite, the capsules seemed to form more slowly, there seemed to be less "specific capsule" and a better opportunity in general for the infection to spread outside the walls of the tubercle. In fact, many of these tubercles seemed to have breaches in the wall due to a growth of the bacilli or to some allergic phenomenon, with a resulting spread of the disease. While there is no way to prove that these episodes are more common in adults than in children, appearances seem to bear it out in fatal cases or cases becoming clinically active. Furthermore, actual pathological evidence seems to show that adult primary infections of this type soon assume the proportions of the reinfection type, while in children there is the tendency to lymphatic spread and generalization and meningitis.

In lesions of adults calcification naturally would be proportionately less, because density of calcification seems to depend largely upon the age of the lesion, caseation and density and thickness of the capsule.

There is another feature concerning the tendency of adult primary infection to localize in the parenchyma. This may be largely speculation but it is certainly an interesting possibility. It is what I have chosen to consider "a nonspecific effect" in people living in large centres of population. It is recognized that nonspecific substances may augment an antibody reaction. It may also catalyze an enzyme or ferment action. It seems possible that nonspecific diseases (colds, whooping cough, measles, scarlet fever, etc.) may change the character of the defense cells so that there is a different and more rapid response to the invasion

of the tubercle bacillus. This may be in the form of greater acute inflammation, necrosis or local fixation of the bacilli. If this be true, then the more primitive the lung conditions of any particular people, the more they should resemble the childhood type of primary tuberculosis. This is exactly what exists; but whether or not this proposed theory is the proper explanation is not established.

The reason for the tendency to localize in the apices in adult primary infections is at present obscure. It has occurred to me, however, for reasons just given, that there may be a slight relative protection in the adult that is not present in the child, so that instead of the germs localizing in the bases they will be swept up the bronchi and expelled, or, as is possible in infection, drift into the less used bronchi in a "drift" action to develop into an infection if the soil is favorable. After the bacilli once become adapted to the tissues a lesion develops. The subapical bronchi are the least used of any, and are the most commonly involved.

Regarding the acute overwhelming types, it seems that these conditions are attributable to some variation in the dosage or virulence of the parasite. Blumenberg (16) has called attention to such types. In experimental animals large dosage seems to produce such violent reactions by sheer quantity of irritant, as shown by Sewall and associates (17), and in the Lübeck disaster, where huge doses were given to infants, the same conditions prevailed as set forth in the reports of Schürmann (18). All of these resemble reinfection types. These cases are not to be confused with the "puberty phthisis" of Aschoff (19), some of which may be truly primary, but most of the acute infiltrative reactions are correctly considered allergic in character. This may also be said of the infiltrations of Assmann (20), which he considered reinfections on mild earlier infections. A similar view is also held by Redeker (21) and Huebschmann (22); but Dietl (23) feels that most of these are primary. The exudative types of lesion are correctly called "reinfection" but they closely follow the first infection. It is significant that Assmann describes small dense fibrous foci around the caseous infiltrates and toward the hilum which he considers as perifocal colonies but does not relate them to any primary type of lesion. These foci correspond to several in this series which, if not primary, are the oldest demonstrable lesions in the body. Many of the foci described by Puhl (24), Simon (25), Redeker (21), Stefko (26) and others are likewise controversial in nature although most of them are reinfections as claimed. It will require either a definite history, a series of tuberculin reactions, serial X-ray

pictures, a complete pathological study, or all of these together before their nature can be definitely established, *because there is no absolute way of telling a primary lesion by pathological appearances alone.* In any event, there is always the possibility of a previous resorption of a primary lesion. While this may occur and escape detection on an antemortem X-ray film, there should be very few to escape a careful pathological search assisted by a postmortem X-ray film.

The "acute benign" types and the hyperplastic lymph node types may be explained on the basis of some peculiar character of the parasite or its relation to the associated bacterial flora. The bovine type of infection is prone to form large "pearly" tubercles which may be due to a persistent "overflowing." The parasites may escape from the capsule, and, perhaps due to a more rapidly growing phase of the microörganism or to a mixture with mutants, cause the peculiar effects in lymph nodes.

The most important observation in this group of cases, as well as those reported before, from the clinical viewpoint, seems to be that marked extension of tuberculous lesions may occur without producing any symptoms. One case actually gained weight and was symptomless during the extension of the disease. The symptomless pathological progression seemed to be a "lag" from an earlier period of overwork. It took months to get under full headway. After the lesions are once opened up there is no way of predicting the extent of the spread from them. Even with no accountable cause, certain lesions seem to light up and gradually cause active disease two to five years after exposure, having a latent period about half the duration found in children.

SUMMARY

In summarizing the conditions prevailing in primary tuberculous infection in adults, it seems that there is a gradual change from the local pneumonic lesions with the lymph node involvement and subsequent haematogenous spread, so characteristic of primary lesions of childhood. The lymph node components tend to become smaller as age advances, and the local lesions, even though they may be small, may overflow early, produce infiltrates which rupture and result in a "secondary type" of disease. At least this seems to prevail in cases coming to autopsy. How many heal without progressive disease is not known. The cause of the local spread is thought to be due to a slower development of the capsule in the adult with a possible augmentation of the growth of the bacilli in certain focal regions. The lack of calcification in such lesions is

perhaps due to the relatively thin capsule as well as the decrease in the age of the tubercle. The great importance of these changes is that they may not be related to apparent disease. It is truly a latent period clinically but an insidious progression pathologically. Pathological activity, therefore, must be recognized as an entity apart from clinical activity.

In huge dosage there may be only an extensive local lesion with only an abortive lymph node lesion. In some, the lymph node lesion seems to be entirely lacking. Occasionally these lesions are benign and clear up with only focal caseation of varying size.

In certain rare cases in white people, but more common in Negroes, there are hyperplastic and overflowing types of primary lymph node lesions that may develop into fibroplastic tumor-like masses.

Owing to the fact that the infection rate is decreasing so rapidly the time seems not far distant when most infections will be in adult life and these atypical forms will be increasingly common.

REFERENCES

(1) Parrot, J. M.: Compt. rend. Soc. de biol., Paris, 1876, p. 308.
(2) Küss, G.: De l'hérédité parasitaire de la tuberculose humaine, Paris, 1898.
(3) Ghon, A.: Primary lung focus of tuberculosis in children, London, 1916.
(4) Ranke, K. E.: Ausgewählte Schriften zur Tuberkulosepathologie, Berlin, 1928.
(5) Birch-Hirschfeld, F. V.: Über den Sitz und die Entwicklung der primären Lungentuberkulose, Deutsches Arch. f. klin. Med., 1899, *64*, 58.
(6) Abrikosoff, A.: Die ersten anatomischen Veränderungen bei Lungenphthise, Virchows Arch. f. path. Anat., 1904, *178*, 173.
(7) Schmorl, G.: München. med. Wchnschr., 1901, p. 1995.
(8) Sweany, H. C.: Studies on the pathogenesis of primary tuberculous infection. II. Tendencies in adult primary tuberculous infection, Amer. Rev. Tuberc., 1933, *27*, 575.
(9) Sweany, H. C.: In press.
(10) Ornstein, G. G., Ulmar, D., and Dittler, E. L.: Benign acute pulmonary tuberculosis, Amer. Rev. Tuberc., 1931, *23*, 223.
(11) Sweany, H. C.: Observations on multiple tuberculous calcification, Ibid., 1935, *32*, 73.
(12) Bernard, L.: Les débuts et les arrêts de la tuberculose pulmonaire, Paris, 1931.
(13) Krause, A. K.: Harvey Society Lectures, 1921–22, *17*, 122.
(14) Loeschcke, H.: Development cicatrization and reactivation of pulmonary tuberculosis in adults, Beitr. z. Klin. d. Tuberk., 1928, *68*, 251.
(15) DuNoüy, L. P.: Biological Time, New York, The Macmillan Co., 1937.
(16) Blumenberg, W.: Kritik der Stadienlehre der Tuberkulose unter besonderer Berücksichtigung des Sekundärstadiums Rankes, Beitr. z. Klin. d. Tuberk., 1929, *7*, 385.
(17) Sewall, H., de Savitsch, E., and Butler, C.: Nodules of experimental tuberculosis in the guinea pig and their relations to immunity, Amer. Rev. Tuberc., 1932, *26*, 1.

(18) SCHÜRMANN, P.: Die anatomischen Befunde bei den in Lübeck verstorbenen Säuglingen, Verhandl. d. deutsch. path. Gesellsch., 1931, *26*, 265.
(19) ASCHOFF, L.: Bericht des Wiesbadener internat. Kongresses, ed. 2, 1921.
(20) ASSMANN, H.: Über die infraclaviculären Infiltrationen im Beginn der Lungentuberkulose von jugendlichen Erwachsenen, Klin. Wchnschr., 1927, *6*, 2128.
(21) REDEKER, F.: Über die infraclaviculären Infiltrate, ihre Entwicklungsformen und ihre Stellung zur Pubertätsphthise, Beitr. z. Klin. d. Tuberk., 1926, *63*, 574.
(22) HUEBSCHMANN, P.: Zur Frage der Infektionswege, Ztschr. f. Tuberk., 1926, *45*, 177.
(23) DIETL, K.: Die chronische Lungentuberkulose im Kindesalter, Beitr. z. Klin. d. Tuberk., 1924, *60*, 325.
(24) PUHL, H.: Über phthisiche Primär-und Reinfektion in der Lunge, Ibid., 1922, *52*, 116.
(25) SIMON, G.: Über die Früherscheinungen der kindlichen Lungentuberkulose, Ibid., 1924, *59*, 529.
(26) STEFKO, W. H.: Die pathologische Anatomie der juvenilen Tuberkulose (Pubertäts phthiseproblem), Ibid., 1928, *69*, 278.

CASE-FINDING[1, 2]

An Evaluation of Various Techniques

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A case-finding program which will discover the maximum number of cases of tuberculosis for the dollars expended is one of the important elements of a plan for the eventual control of tuberculosis. The success of the entire program depends upon prevention of the spread of the tubercle bacillus, by segregation of cases already infectious and by discovery and treatment of early cases before they have become infectious. The importance of using a case-finding method which will yield the largest number of cases is, therefore, apparent.

In 1934, I stated (1), "The X-raying of the entire population once or twice a year might result in the discovery of every case of tuberculosis. This being impractical, it is urged that those physicians charged with the responsibility of tuberculosis control intensify their efforts among cases, contacts, and patients referred from private practice by physicians." The importance of examining other selected groups, such as employees in certain industries, unskilled laborers, and adults in the lower economic strata, was also stressed.

The experience of the New York State Department of Health since that time has confirmed my opinion that tuberculosis case-finding should be administered by these two methods.

The first method, namely, the examination of contacts and of patients referred by physicians because of suspicious symptoms, has been most profitable in the yield of new cases of reinfection or adult type of pulmonary tuberculosis, and has afforded a demonstration that the examination of adults in this group is considerably more important than the routine examination of school children as a means of discovering new cases.

The service which provides these examinations of contacts and referred

[1] Presented at a session of the Social Work Section at the 34th annual meeting of the National Tuberculosis Association, Los Angeles, California, June 22, 1938.

[2] From the New York State Department of Health, Division of Tuberculosis, Albany, New York.

patients has been developed as the result of painstaking effort, over a period of eighteen years, to integrate public control of tuberculosis with the private practice of medicine. The success of such a program depends upon the realization that it must include all the scientific features necessary for diagnosis, and that the professional standards must be of a calibre which will encourage the practicing physicians to refer to the clinics all patients in need of the service. To be most effective, the service must also be brought figuratively to the doorstep of the people.

This type of case-finding is conducted in the out-patient departments of the four State tuberculosis hospitals, each of which is located in the geographic and population centre of a group of seven or eight counties, and in the itinerant clinics held by these hospitals in all sections of the counties served. Prior to the opening of the four new hospitals, we were able to offer clinic service in these newly established hospital areas only once or twice a year. Since the hospitals have been opened, expert facilities are constantly available to the physicians, with a minimum of inconvenience to their patients. If a person has no private physician, or cannot afford one, an admission card may be obtained from any local health officer. There is no charge for the clinic service. Following the examination, a detailed report of the findings and recommendations is mailed to the referring physician and a copy to the local public health nurse.

That such a method is not only workable but profitable is demonstrated, first, by the fact that practically 100 per cent of the general practitioners in the areas participate in the program, and, second, by the fact that more cases of tuberculosis are discovered by the examination of contacts and of patients referred by family physicians for diagnosis than by any other generally practiced method of case-finding.

The year 1937 was the first complete year of service in the out-patient departments and field clinics of the four State tuberculosis hospitals. A total of 15,308 examinations were made of 11,928 individuals, or about one per cent of the population of the areas served. The distribution of these individuals by sex, history of contact, and previous examination is shown in table 1.

The total number of persons examined was almost evenly divided into contacts, that is, persons with a known history of exposure to a case of tuberculosis, and noncontacts, or persons who gave no history of known contact with a case but who were referred because of suspicious

symptoms. There was a smaller proportion of contacts among males (44 per cent) than among females (51 per cent).

TABLE 1

Individuals examined, by sex, history of contact and previous examination

	NUMBER			PER CENT		
	Total	Male	Female	Total	Male	Female
Total examined	11,928	5,364	6,564	100.0	100.0	100.0
Contacts	5,713	2,357	3,356	47.9	43.9	51.1
Noncontacts	6,215	3,007	3,208	52.1	56.1	48.9
New patients	9,098	4,149	4,949	100.0	100.0	100.0
Contacts	3,770	1,575	2,195	41.4	38.0	44.4
Noncontacts	5,328	2,574	2,754	58.6	62.0	55.6
Reëxamined patients	2,830	1,215	1,615	100.0	100.0	100.0
Contacts	1,943	782	1,161	68.7	64.4	71.9
Noncontacts	887	433	454	31.3	35.6	28.1

TABLE 2

Individuals examined, by age and sex, according to history of previous examination and contact

AGE AND SEX	TOTAL EXAMINED	NEW PATIENTS		REËXAMINED PATIENTS	
		Contacts	Non-contacts	Contacts	Non-contacts
Both sexes—all ages	11,928	3,770	5,328	1,943	887
Under 15 years	3,535	1,144	1,385	831	175
15–24 years	2,851	966	1,199	491	195
25–44 years	3,734	1,147	1,794	456	337
45 years and over	1,808	513	950	165	180
Males—all ages	5,364	1,575	2,574	782	433
Under 15 years	1,760	567	700	397	96
15–24 years	1,159	378	512	192	77
25–44 years	1,465	417	772	132	144
45 years and over	980	213	590	61	116
Females—all ages	6,564	2,195	2,754	1,161	454
Under 15 years	1,775	577	685	434	79
15–24 years	1,692	588	687	299	118
25–44 years	2,269	730	1,022	324	193
45 years and over	828	300	360	104	64

Only 41 per cent of the 9,098 new patients were contacts of cases, while more than two-thirds of the 2,830 who were reëxamined were con-

tacts. The lower percentage of contacts among males than among females is observed among old as well as new patients.

The age distribution of old and new patients examined, classified by sex and history of contact, is shown in table 2.

Nearly one-third of the total number examined fell in the age group twenty-five to forty-four years (31.3 per cent), a percentage only slightly higher than in the age group under fifteen (29.6).

TABLE 3

Cases of tuberculosis and rates (active cases found in each 100 patients examined) by age, sex, history of previous examination, and contact

AGE AND SEX	ALL PATIENTS		NEW PATIENTS						REEXAMINED PATIENTS					
	Total		Total		Contacts		Noncontacts		Total		Contacts		Noncontacts	
	Number	Rate	Number	Rate	Number	Rate	Number	Rate	Number	Rate	Number	Rate	Number	Rate
Both sexes—all ages	349	2.9	319	3.5	127	3.4	192	3.6	30	1.1	20	1.0	10	1.1
Under 15 years	4	0.1	4	0.2	2	0.2	2	0.1	—	—	—	—	—	—
15 years and over	345	4.1	315	4.8	125	4.8	190	4.8	30	1.6	20	1.8	10	1.4
15–24 years	76	2.7	62	2.9	31	3.2	31	2.6	14	2.0	9	1.8	5	2.6
25–44 years	153	4.1	143	4.9	61	5.3	82	4.6	10	1.3	6	1.3	4	1.2
45 years and over	116	6.4	110	7.5	33	6.4	77	8.1	6	1.7	5	3.0	1	0.6
Males—all ages	171	3.2	162	3.9	48	3.0	114	4.4	9	0.7	7	0.9	2	0.5
Under 15 years	1	0.1	1	0.1	1	0.2	—	—	—	—	—	—	—	—
15 years and over	170	4.7	161	5.6	47	4.7	114	6.1	9	1.2	7	1.8	2	0.6
15–24 years	23	2.0	19	2.1	11	2.9	8	1.6	4	1.5	3	1.6	1	1.3
25–44 years	75	5.1	72	6.1	22	5.3	50	6.5	3	1.1	2	1.5	1	0.7
45 years and over	72	7.3	70	8.7	14	6.6	56	9.5	2	1.1	2	3.3	—	—
Females—all ages	178	2.7	157	3.2	79	3.6	78	2.8	21	1.3	13	1.1	8	1.8
Under 15 years	3	0.2	3	0.2	1	0.2	2	0.3	—	—	—	—	—	—
15 years and over	175	3.7	154	4.2	78	4.8	76	3.7	21	1.9	13	1.8	8	2.1
15–24 years	53	3.1	43	3.4	20	3.4	23	3.3	10	2.4	6	2.0	4	3.4
25–44 years	78	3.4	71	4.1	39	5.3	32	3.1	7	1.4	4	1.2	3	1.6
45 years and over	44	5.3	40	6.1	19	6.3	21	5.8	4	2.4	3	2.9	1	1.6

The results of the examinations in yield of new cases are shown in table 3.

Only 4 of the total of 349 new cases of clinically significant pulmonary tuberculosis occurred among the 3,535 children under fifteen years of age. The rate for the group fifteen years of age and over, 4.1 cases per 100 persons examined, was 41 times the rate among children under fifteen.

There were no cases found among the 1,006 reëxamined patients under fifteen years of age and only 30, or a rate of 1.6 per cent, among reëxamined patients over fifteen. The most important group from the standpoint of number of cases was, therefore, the new patients over fifteen years of age. Of the 349 new cases discovered, 315 occurred in this group, representing a yield of 4.8 per cent. The rate was the same among both contacts and noncontacts. The rate for male noncontacts over fifteen (6.1), however, was noticeably higher than the corresponding rate for females (3.7), due to higher rates in the age groups over twenty-five. The rates among contacts over fifteen were almost equal for males and females in each age group.

The yield of cases per 100 new patients examined increased with age, among both males and females. The greatest yield was found in the group of new male patients over forty-five (8.7 per cent). The highest yield among new female patients was 6.1 per cent.

It should be noted that the total yield of 4.1 cases per 100 persons examined in the adult ages occurred in counties in which there is believed to be no unusual prevalence of tuberculosis. The death rate from tuberculosis in those counties was only 30 per 100,000 population in 1937.

The stage of disease at the time of diagnosis, shown in table 4, varies with age, sex and history of contact and previous examination. Of the total number of new cases, 54 per cent were minimal, 25 per cent moderately advanced and 21 per cent far advanced. Among males, the percentage of minimal cases was only 46, compared with 61 per cent among females.

This difference between males and females was chiefly due to differences in the age groups fifteen to twenty-four and twenty-five to forty-four years, where the percentages of minimal cases were 52 and 41, respectively, for males, compared with 60 and 67 per cent among females. The percentage of minimal cases in the age group forty-five years and over was practically equal for the two sexes, 49 for males and 50 for females. As there were only 4 cases under fifteen years of age the results in this age group were not significant.

The higher proportion of minimal cases among females may be partly due to the larger proportion of contacts and reëxamined patients, among whom the disease is more often discovered in the early stages than among persons referred for the first time because of suspicious symptoms. However, a large part of the difference is due to the fact that male contacts are less likely than female contacts to appear for examination during the early stage of the disease.

Among female contacts examined for the first time, 73.4 per cent of the cases discovered were in the minimal stage, compared with 52.1 per cent among male contacts examined for the first time. A higher percentage of minimal cases was found among new female contacts than among males in each age group over fifteen. The percentage of minimal cases among those found in new female patients who were not contacts (39.7) was only slightly below the corresponding figure for males (41.2).

TABLE 4

Cases of tuberculosis discovered, by stage of disease, according to sex and history of previous examination and contact

SEX AND HISTORY	TOTAL		MINIMAL		MODERATELY ADVANCED		FAR ADVANCED	
	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent
Both sexes—total	349	100.0	187	53.6	87	24.9	75	21.5
New patients	319	100.0	161	50.5	83	26.0	75	23.5
Contacts	127	100.0	83	65.4	32	25.2	12	9.4
Noncontacts	192	100.0	78	40.6	51	26.6	63	32.8
Reëxamined patients	30	100.0	26	86.7	4	13.3	—	—
Contacts	20	100.0	16	80.0	4	20.0	—	—
Noncontacts	10	100.0	10	100.0	—	—	—	—
Males—total	171	100.0	79	46.2	49	28.7	43	25.1
New patients	162	100.0	72	44.4	47	29.0	43	26.5
Contacts	48	100.0	25	52.1	16	33.3	7	14.6
Noncontacts	114	100.0	47	41.2	31	27.2	36	31.6
Reëxamined patients	9	100.0	7	77.8	2	22.2	—	—
Contacts	7	100.0	5	71.4	2	28.6	—	—
Noncontacts	2	100.0	2	100.0	—	—	—	—
Females—total	178	100.0	108	60.7	38	21.3	32	18.0
New patients	157	100.0	89	56.7	36	22.9	32	20.4
Contacts	79	100.0	58	73.4	16	20.3	5	6.3
Noncontacts	78	100.0	31	39.7	20	25.6	27	34.6
Reëxamined patients	21	100.0	19	90.5	2	9.5	—	—
Contacts	13	100.0	11	84.6	2	15.4	—	—
Noncontacts	8	100.0	8	100.0	—	—	—	—

This failure to discover the same proportion of minimal cases among male contacts as among female contacts may be a result of the fact that all of the field clinics are conducted at hours when most men are unable to attend because of business obligations. The age distribution of males and females examined, shown in table 2, with lower percentages in the groups fifteen to twenty-four and twenty-five to forty-four among males

than among females, also suggests that it is more difficult for adult males to attend the clinics.

The cost of finding new cases, an important item for consideration in any tuberculosis program, obviously is least in the group with the highest yield of new cases. The 15,000 examinations, including X-ray films, in the out-patient departments and clinics of the four State tuberculosis hospitals in 1937, were made at a cost of four dollars per examination. The expense per individual, including reëxaminations, is conservatively

TABLE 5

Cost of finding new cases, according to age and history of previous examination

	NUMBER EXAMINED	ESTIMATED COST AT $5 PER PERSON	NUMBER OF NEW CASES	COST PER CASE
All patients—all ages	11,928	$59,640	349	$171
Under 15 years	3,535	17,675	4	4,419
15 years and over	8,393	41,965	345	122
15–24 years	2,851	14,255	76	188
25–44 years	3,734	18,670	153	122
45 years and over	1,808	9,040	116	78
New patients—all ages	9,098	45,490	319	143
Under 15 years	2,529	12,645	4	3,161
15 years and over	6,569	32,845	315	104
15–24 years	2,165	10,825	62	175
25–44 years	2,941	14,715	143	103
45 years and over	1,463	7,315	110	67
Reëxamined patients—all ages	2,830	14,150	30	472
Under 15 years	1,006	5,030	—	—
15 years and over	1,824	9,120	30	304
15–24 years	686	3,430	14	245
25–44 years	793	3,965	10	397
45 years and over	345	1,725	6	288

estimated at five dollars. The cost of finding new cases in various groups, on this basis, is shown in table 5.

The group with the highest yield was that of new patients in the oldest age classification, forty-five years and over, where the cost was $67. In the larger group of new patients fifteen years of age and over, cases were discovered at a cost of $104 each. The cost was considerably greater among patients who had been previously examined, $304 per case, over fifteen years of age. The expenditure of $5,030 for all reëxminations of persons under fifteen years of age yielded no new cases.

The most expensive group was that of children under fifteen, where there were only 4 cases found, at a cost of $4,419 each. Considering only new patients under fifteen, among whom all of the 4 cases were found, the cost was still very high, $3,161 per case.

Whether the cost of an examination is $1.00 or $5.00, it should be apparent that it is about forty times more expensive to discover a case of pulmonary tuberculosis among children who are contacts or have symptoms than among adults who are contacts or who have symptoms.

The second method of case-finding recommended, the examination of special groups, has produced varying results in the yield of new cases. However, the experience in such studies, in addition to the actual case-finding service, is valuable for several purposes. It provides evidence of the prevalence of tuberculosis in various groups, indicating where future case-finding surveys may be most economically conducted; it furnishes data for continued studies of the epidemiology and pathogenesis of tuberculosis, and acts as a guide in the planning of future epidemiological studies. The conduct of the surveys is also valuable as an instrument of public health education.

Since we are convinced, as a result of our consultation experience in the past several years, that good case-finding should emphasize the examination of adults rather than children, most of the special surveys made by the New York State Department of Health have been surveys of adult groups. This emphasis upon the examination of adults in a case-finding program, however, should not be interpreted as an argument against the inclusion of children in groups being studied for epidemiological or other research purposes. Among the groups studied by the Department are:

GROUP	NUMBER EXAMINED	CASES	CASES PER 100 EXAMINED
General hospital admissions (adults)	3,977	47	1.2
Foundry workers	4,754	42	0.9
Food production plants	1,531	2	0.1
Normal school students (ages 17–21)	6,021	17	0.3
Newark State School (feeble-minded—all ages)	2,321	62	2.7

With the exception of the workers in food production plants, the examination of these groups is being continued, and the results will be published at a later date.

Of special significance is the study being made of admissions to fourteen general hospitals throughout upstate New York, which not only

shows the highest yield, with the exception of Newark State School, but also shows that a surprisingly large number of cases of tuberculosis are admitted to hospitals without being recognized. This study will continue until 5,000 persons have been examined. No children are included, nor any persons in whom there was a previously known tuberculous lesion. Of the 47 new active cases already discovered, 19 had evidence in their hospital charts which might have led the attending physician to diagnose the case before discharge. However, 28, or 0.7 per cent of adult admissions, were found to have active tuberculosis, although there was no evidence in the hospital records which indicated that tuberculosis was suspected at the time of admission. If the same condition prevailed throughout the United States, about 45,000 unrecognized cases of tuberculosis were admitted to general hospitals during 1937.

CONCLUSIONS

The evidence presented points definitely to special groups in the population where case-finding efforts will yield the greatest returns at a minimum of expense.

It proves that there is still to be found a medium for case-finding which will be as consistently productive as examination of adult contacts and noncontacts who are referred by physicians because of symptoms. The number of cases found among children under fifteen, examined because of contact or symptoms, was almost negligible. In case-finding programs, therefore, greater emphasis must be placed upon securing the examination of adult contacts, even to the exclusion of children, when such a choice has to be made. It is important, also, that no stone should be left unturned to secure the coöperation of the practicing physicians in obtaining the examination of all adults who present symptoms which might even remotely be referred to the chest.

The study of stage of disease among contacts and referred patients shows, as would be expected, that contacts yield a larger percentage of cases in the minimal stage than noncontacts referred because of suspicious symptoms. The percentage of minimal cases, however, is considerably higher among female contacts than among male contacts, indicating that greater effort should be made to secure examination of male contacts in the early stage of the disease.

It is obvious that groups of adults other than the above should be explored. Otherwise, many hidden foci of infection will spread the disease. The groups which may be expected to yield the greatest re-

turns in new cases may be determined by an objective study of available morbidity and mortality data in each locality. Race, sex, age, place of residence and industrial factors deserve serious consideration in planning the study of selected groups.

The combination of a routine consultation-type clinic service and the X-raying of selected adult groups should provide the medium for an optimum case-finding program.

REFERENCE

(1) PLUNKETT, R. E.: Relative values in tuberculosis case finding, Amer. J. Pub. Health, 1934, *24*, 511.

COCCIDIOIDES INFECTION[1,2]

A Case of Primary Infection in the Lung with Cavity Formation and Healing

O. J. FARNESS AND CHARLES W. MILLS

Fungus coccidioides infection, although no longer an uncommon disease in California, is still a rarity elsewhere. Since its recognition in 1892 by Wernike (1) and Posados of Buenos Aires, 450 cases (2) with 224 deaths have been recorded to July 1, 1936 in the State of California. With a few exceptions, this represents the cases reported in this country. Why this disease is concentrated in California with the majority of cases coming from the San Joaquin Valley and Los Angeles County is still open to discussion.

Coccidioidosis is a disease produced by a specific fungus, *Coccidioides immitis*. Both man and animal are susceptible to infection, but as yet, except experimentally, no man to man, animal to animal, or animal to man transmission has been definitely observed. The fact that the majority of cases occur in persons coming in contact with the soil and its products would suggest soil as the most probable source of infection. The portal of entry may be through the skin or gastrointestinal tract but in the majority of cases infection is contracted through inhalation (3, 4, 5, 6). Although, like tuberculosis, the disease may involve any organ in the body, the skin, lungs, bones, lymph nodes and meninges are most commonly affected. The general mortality rate once estimated to be 100 per cent has dropped to less than 50 per cent as the number of recognized cases has increased. The incubation period is still in doubt although cases in which the probable time of infection is known would indicate that it is between one and three weeks.

A very complete report on the history, aetiology, symptomatology, diagnostic laboratory procedure and epidemiology of coccidioidal granuloma may be found in Special Bulletin No. 57 issued by the California Department of Public Health (3). It is sufficient to point out here that the disease is protean in its clinical manifestations and that its

[1] From The Desert Sanatorium of Southern Arizona, Tucson, Arizona.

[2] Presented at the third annual meeting of the American Academy of Tuberculosis Physicians, San Francisco, California, June 17, 1938.

mimicry of tuberculosis and blastomycosis is such that a diagnosis can be made with certainty only by finding the characteristic spherules with double contoured capsules in the tissues, pus or sputum and confirming this finding by culture and animal inoculation.

In the pulmonary form of the disease, initial symptoms are those of a hard "cold" suggestive of influenza or bronchopneumonia. Cough and sputum which may be blood-stained, chills, fever, night sweats, loss of weight and strength, malaise, anorexia, weakness and general debility are present in varying degrees. Blood eosinophilia and erythema nodosum are frequently observed.

The present case is reported because it developed outside of California and because very few clear-cut cases of primary involvement of the lungs are recorded (6). No cases with cavity formation and subsequent healing by fibrosis are available for study. The very close similarity to acute tuberculosis and blastomycosis and the difficulty in differential diagnosis become evident. This case is still more unusual in view of the extensive pulmonary pathology and the virulence of the invading micro-organisms as opposed to the benign clinical course.

Case Report

P. T., a white male, aged 15 years, Michigan born, gave a history of severe nasal sinus disease and bilateral middle-ear infection over a period of years. In 1928 he had measles, mumps, a bilateral mastoidectomy and pneumonia. Since 1934 he had been attending a private school near Tucson because of the difficulty of controlling the head infections at home in Michigan.

On November 20, 1936, an unidentified insect stung the patient's finger. For half an hour following this sting he experienced acute pain and for a week the finger was numb. Sometime between December 10 and December 15 he contracted a "sinus cold." (It seems improbable that there was any direct relation between the sting on the finger and the so called cold. He was at this same time in contact with the soil through such athletic pursuits as football, riding and rifle shooting.) On January 4 he returned to Tucson from a Christmas holiday at home with a severe "cold," an acute sinus flare-up and discharging ears. He was ordered to the school infirmary and treated for his sinus and ear infection. He was feeling well and had no temperature rise but was coughing and raising some sputum. On January 12 he complained of pains in the right chest. On January 14 the chest was examined and no auscultatory changes were noted. On January 16 an X-ray film (figure 1) was made of the chest which revealed a 3 x 4 cm. cavity in the right infraclavicular region with a patch of heavy infiltration immediately above the cavity. On January 22 a test of concentrated sputum was negative for tuber-

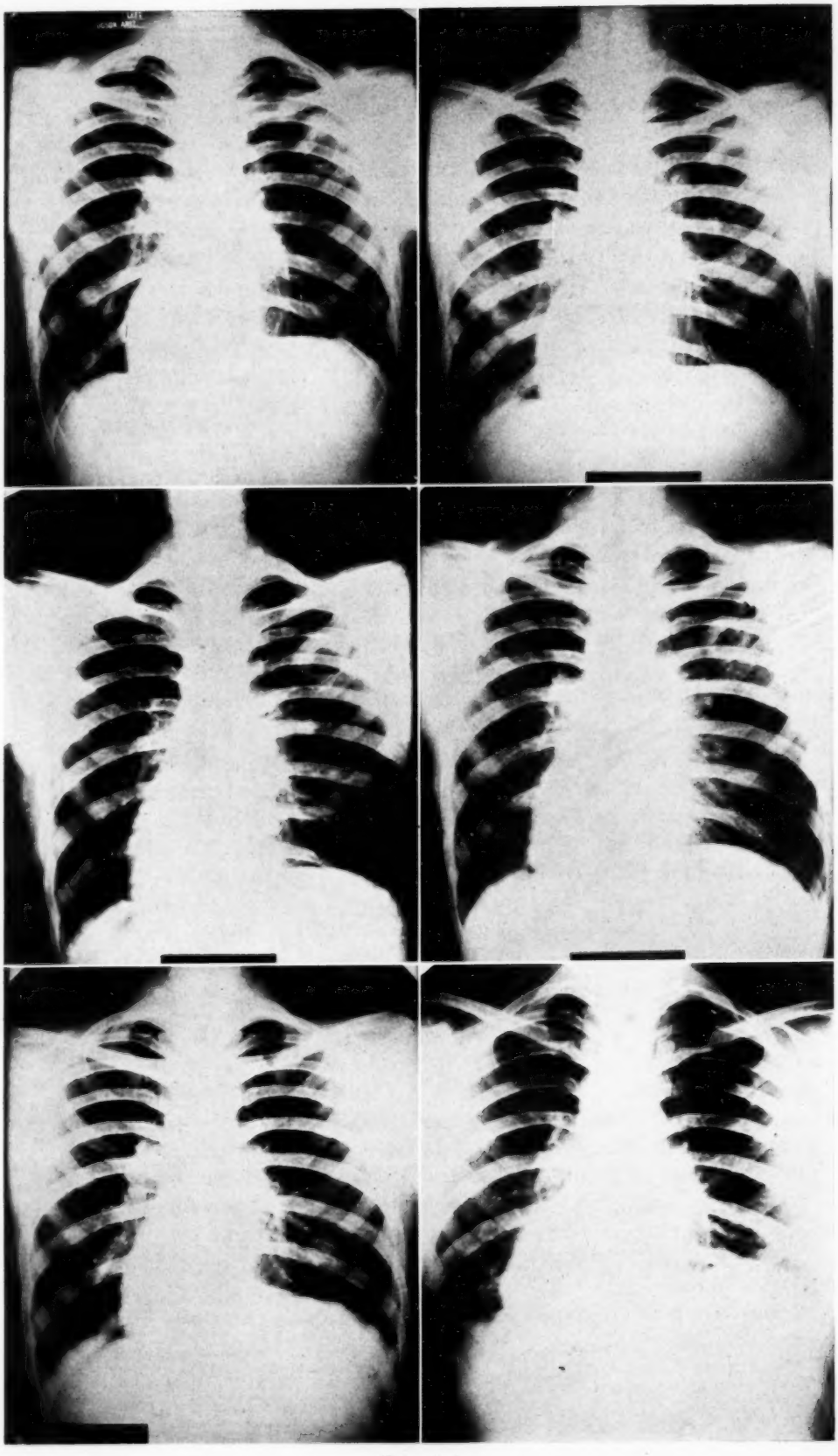

FIG. 1

FIG. 2

FIG. 3

FIG. 4

FIG. 5

FIG. 6

FIGS. 1–6

cle bacilli. A second X-ray film made February 8 showed the cavity to be of the same size but the patch of infiltration had disappeared and the wall of the cavity was exceedingly thin. The patient was feeling well and had no cough or sputum. After further rest a third X-ray film was made February 19 which showed the cavity to be larger and a reappearance of the patch of infiltration above the cavity. In addition there was extensive soft infiltration in the region of the right middle lobe and fluid in the lower left chest.

The patient was admitted to The Desert Sanatorium on February 20 with no other complaints than the "cold" that had been bothering him for two months. He reluctantly admitted that he had coughed and raised a little and that once the sputum was blood streaked. There had been no weight loss. Except for a period of about a week during the Christmas holidays when he ran a low grade fever of from 99° to 99.2° F., there had been no elevation of temperature at any time. There had been no chills or night sweats.

It was difficult to make a correlation between the striking lack of constitutional symptoms and the extent of the pulmonary pathology. None the less, we felt at this time that we were dealing with an asymptomatic, acute, rapidly spreading tuberculosis and that the best procedure was to collapse the right lung. Following an X-ray film on February 22 (figure 2), which showed a spread to the left lower lobe, artificial pneumothorax was instituted on the right.

The laboratory findings on February 22 were as follows: haemoglobin, 16 g.; erythrocyte count 5,380; leucocytes 10,500 with 56 per cent neutrophiles, 14 per cent lymphocytes, 3 per cent monocytes and 27 per cent eosinophiles. The blood sedimentation rate by the Westergren method was 7 mm. at the end of an hour. A 24-hour sputum collection weighed 20 g. It was thick, mucopurulent and contained some blood. On repeated examination

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FIG. 1. January 16, 1937. Shows a 3 x 4 cm. cavity in the right infraclavicular region with a patch of heavy infiltration immediately above the cavity and slight clouding toward the periphery of the lungs from the first to fifth rib. There is thickening of both hilar shadows.

FIG. 2. February 22, 1937. Shows, in addition to the exudative lesion immediately above the cavity, extensive soft infiltration in the region of the right middle lobe and a large patch of soft infiltrate in the left lower lobe.

FIG. 3. February 24, 1937. Shows a partial collapse of the right lung. The more definitely outlined cavity is of the same size but altered in shape and containing fluid. There is clearing of the infiltration surrounding the cavity as well as clearing of the soft exudative lesion on the left.

FIG. 4. March 1, 1937. Shows more compression of the right lung but with the cavity held open by an adhesion. The cavity is somewhat smaller in size. There has been further clearing of the infiltration around the cavity as well as more absorption of the soft lesion on the left.

FIG. 5. March 24, 1937. Shows a reduction in the size of the cavity and almost no surrounding infiltration.

FIG. 6. August 4, 1937. Shows the cavity closed.

the sputum contained no acid-fast bacilli but did contain some spherules with double contoured capsules filled with endospores suggesting *C. immitis*. On culture the microörganism grew out as a fungus with long mycelia. Of three guinea pigs inoculated, two with the pure culture and one with concentrated sputum, all showed early orchitis and, at autopsy, the typical tubercular lesions and spherules of coccidioides infection. *C. immitis* was grown in pure culture from the lesions. The intracutaneous tuberculin test was negative to 0.1 mg. OT. The coccidioidin skin test, performed at a later date, was strongly positive.

The patient was in the hospital two weeks on complete bed-rest. None of the drugs advocated for the treatment of coccidioidal granuloma were prescribed. He continued to gain in weight. His sputum decreased to 3 and 4 g. in 24 hours. He felt well and was irked at having to remain in bed. An X-ray film made February 24 (figure 3), after the second refill, showed a 25 per cent collapse of the right lung. The cavity was the same size although altered in shape and containing fluid. There was clearing of the surrounding infiltration as well as a clearing of the soft lesion on the left. On March 1 the X-ray film (figure 4) showed more compression of the right lung but with the cavity held open by an adhesion. There was further clearing of the parenchymal infiltration around the cavity and also more absorption of the soft lesion on the left. At this time, with the diagnosis definitely established, the artificial pneumothorax was discontinued for fear of producing an empyema.

On March 6 the patient was referred to Dr. H. P. Jacobson of Los Angeles because of his interest in and work on fungus diseases. Under his direction, in addition to bed-rest, the patient was started on a course of specific vaccine therapy. Resolution and healing of the lung progressed. The blood eosinophil count on March 10 was 6 per cent. An X-ray film made March 24 (figure 5) showed the cavity reduced in size with practically no surrounding infiltration. The left lung was clear. Improvement continued and the cough and sputum had by now entirely disappeared. An X-ray film made August 4 (figure 6) showed the cavity to be closed. At this time the patient was discharged to his home physician in Michigan, feeling well and up and about most of the day.

A communication from the patient dated November 13, 1937, revealed that he was still receiving vaccine therapy and was not yet on full activity. An X-ray film made in October showed further contraction of the scar at the site of the cavity.

COMMENT

The early diagnosis and complete recovery in this case led us to believe that we were dealing with an acute primary infection of the lungs with *C. immitis*. Search of the literature revealed many cases of lung infec-

tion with *C. immitis* but until recently the cases reported with pulmonary involvement have always been part of a generalized infection and the prognosis was invariably bad.

Dickson (6) has recently reported five cases of primary involvement of the lung, the first recorded. Four of the cases were exposed to infection in the San Joaquin Valley, the fifth occurred in a laboratory worker. In all, the onset was characterized by pulmonary involvement with fever, cough and sputum. Increase in eosinophil count (3 to 7 per cent) and erythema nodosum occurred with noticeable regularity. X-ray diagnosis on first examination was tuberculosis. The intracutaneous skin test with specific antigen in two of the cases on which the test was performed was positive. All of the cases recovered. By comparison, our own case differed in the paucity of constitutional symptoms, the higher eosinophil count (27 per cent), the presence of a large cavity, and the absence of any signs of erythema nodosum during the course of the disease. We have been unable to find any other case of primary lung involvement with demonstrable cavity.

The early pulmonary manifestations of fungus Coccidioides bear out the contention of many writers that the infection is most often respiratory. If pulmonary infection is the immediate result of the initial exposure, then the fatal, destructive process of coccidioidal granuloma is a secondary manifestation as a result of dissemination from the primary focus. This early phase of the disease is suggestive of first infection tuberculosis, in that healing is the rule. In contrast to tuberculosis, the onset is usually more acute, tissue destruction is greater and healing is more rapid.

A number of cases of an unpublished symptom complex originating in the San Joaquin Valley of California and popularly referred to as "San Joaquin or Valley Fever," characterized at the onset by symptoms and signs of a "cold" or bronchopneumonia and followed in seven to ten days by an outbreak of erythema nodosum, are now being investigated by Dr. Joe Smith (6) of Bakersfield, California. The usual course of the disease has been complete recovery in a few months' time. *C. immitis* has been recovered from the sputum in some of the cases. The outcome of this investigation will be watched with great interest.

Perhaps many cases of so called severe cold or influenza, often with signs of bronchopneumonia, are incompletely diagnosed. The heretofore pessimistic outlook for fungus Coccidioides infection may, with earlier diagnosis, be due for a change.

The treatment of this infection in general has been extremely varied and no definite specific results have been noted from any drug therapy. Antimony and potassium tartrate intravenously and colloidal copper intramuscularly have been used without consistently satisfactory results. The use of vaccine as advocated by Jacobson (7) cannot yet be properly evaluated. More recently sulfanilamide has been tried. Judging from the records of the diagnosed primary pulmonary forms of the disease, the tendency is to heal. A strict regimen of bed-rest following the routine used in tuberculosis is for the present the basis of treatment. The claims for drug and vaccine therapy have not been established.

Because the symptom complex of early fungus coccidioides infection cannot rightly be called coccidioidal granuloma, Dickson has proposed the word "coccidioidomycosis" to include all cases of infection with fungus Coccoidioides with further classification into three divisions: (*1*) primary inspiratory, to include the cases herein described; (*2*) primary cutaneous, those cases infected through the skin; and (*3*) secondary or late, those cases with generalized infection and granulomatous lesions. This classification also awaits further development.

SUMMARY

A case of pulmonary infection with *Coccidioides immitis*, probably primary in the lung, is reported. Interesting features were the absence of constitutional symptoms, a high eosinophilia and, heretofore unreported, early cavity formation. Treatment was rest, artificial pneumothorax, and a specific vaccine. Healing was rapid and after more than ten months' interval (when this report was made) the disease appeared cured.

Addendum

Since this paper was presented our attention has been called by Dr. Max Pinner, who performed the autopsy, to an unreported fatal case of pulmonary coccidioides with cavity which is in the records of this hospital. The diagnosis was made at autopsy.

H. S., a white male, aged 67 years, living within the city limits of Tucson, was admitted to the hospital April 12, 1932, with signs and symptoms of bronchopneumonia. Ten days previous to this he had contracted a severe cold. On the third day following admission, the patient died. Autopsy revealed multiple bronchopneumonic foci throughout both lungs, many with necrotic centres, and an abscess measuring 2.5 cm. in diameter was present in the midportion of the left lung. *Coccidioides immitis* was recovered from

the abscess and some of the bronchopneumonic foci. No foci of infection with *Coccidioides immitis* could be found in any other part of the body.

REFERENCES

(1) WERNIKE, R.: Über einen Protozoenbefund bei Mycosis fungoides, Centralbl. f. Bakt., 1892, *12*, 856.
(2) Coccidioidal granuloma in California in 1934–35, California & West. Med., 1937, *46*, 282.
(3) RIXFORD, E., DICKSON, E. C., AND BECK, M. D.: Special Bulletin No. 57 issued by the California Dept. of Public Health, Sacramento, California, Department of Vital Statistics, 1931.
(4) JACOBSON, H. P., SCHAMBERG, J. F., AND MORROW, H.: Fungus disease, Charles C. Thomas, Springfield, Ill., 1932.
(5) CARTER, B. A.: Coccidioidal granuloma, Am. J. Roentgenol., 1931, *25*, 715.
(6) DICKSON, E. C.: "Valley Fever" of the San Joaquin Valley and fungus Coccidioides, California & West. Med., 1937, *47*, 151.
(7) Personal communication.

BLASTOMYCOSIS[1,2]

(American Blastomycosis, Gilchrist's Disease)

I. A Review of the Literature

DONALD S. MARTIN AND DAVID T. SMITH

Infection with *Blastomyces dermatitidis*, although found in at least twenty-eight states, probably is more common than is indicated by the published reports. Many patients with generalized blastomycotic infections, especially those without the characteristic skin lesions, are not diagnosed until careful microscopical postmortem study. The antemortem clinical symptoms as well as the gross postmortem lesions frequently are thought to be tuberculous (62, 154, 235). Patients with chronic pulmonary infections, in whom tubercle bacilli or other organisms cannot be found, should be intensively studied for *Blastomyces*, as the prognosis is not so grave if the correct diagnosis is made and therapy started before the patient has been overwhelmed by the disease.

HISTORICAL

Gilchrist, in June, 1894 (86), at a meeting of the American Dermatological Association, described large, double-contoured, round and oval parasites in sections of skin from a verrucous lesion on the hand of a Philadelphia patient. No cultures were obtained. In July of the same year, Buschke and Busse (35), in Germany, isolated a yeast-like fungus from a tibial abscess of a patient who had generalized lesions. The cultures and necropsy were later described in more detail by Busse (36, 37). Since the organism isolated from this patient grew as a yeast and possessed fermentative powers, the disease was described as a case of "saccharomycosis."

Gilchrist (87) then published a very complete description of the biopsy findings in his patient, naming the disease *blastomycetic dermatitis* since

[1]Presented in part at a session of the Clinical Section at the 32nd annual meeting of the National Tuberculosis Association, New Orleans, Louisiana, April 24, 1936.

[2]From the Departments of Medicine and Bacteriology, Duke University School of Medicine and Duke Hospital,[3] Durham, North Carolina.

[3]Aided by a grant from the John and Mary R. Markle Foundation.

the morphological appearance of the organism in section resembled the fungus described by Busse. Gilchrist and Stokes (89) in 1896 reported another patient with skin lesions on the face, sections of which showed the same type of budding organism as was seen in Gilchrist's first case, and from which they were able to obtain cultures. On artificial media, however, the fungus grew as a mold and was shown to have no fermentative ability. This fungus was then recognized to be quite different from the yeast-like organism described by Busse and was tentatively classified as an *Oidium*. In a later paper by Gilchrist and Stokes (90) the fungus was named *Blastomyces dermatitidis* because the authors considered that the new organism probably belonged to that group of "wild yeasts" some of which had been described as nonfermenting, mycelia-producing organisms.

Since this time the term blastomycosis has been applied to infection with either fungus, and the disease has generally been classified and referred to as American blastomycosis, which is caused by the fungus which grows as a mold, and European blastomycosis, in which the aetiological agent is a yeast-like fungus in culture. Although the term blastomycosis is applicable to both infections, since both types of fungi appear in the tissues as budding forms, less confusion is apt to result if the term blastomycosis is reserved for those infections caused by Gilchrist's organism (*Blastomyces dermatitidis*) and the term cryptococcosis applied to infections caused by the yeast-like fungus of the genus *Cryptococcus* (*Torula*).

Since the publication by Gilchrist and Stokes (90) in 1898, nineteen new names for the fungus have appeared in the literature.[4] From studies carried out in this laboratory (55) it is probable that the fungi for which all these names have been used are the same, and we prefer the name *Blastomyces dermatitidis* as most suitable.

The present study is based only upon those cases falling into the classification of American blastomycosis, or Gilchrist's disease.

Three hundred and forty-seven case reports have been studied, including the 13 patients described in this paper (table 1). Only 80 (23 per cent) of these cases can be considered as unquestionably proved to be caused by *Blastomyces dermatitidis*.[5] One hundred and sixty-three cases

[4]References 2, 13, 18, 32, 33, 43, 68, 119, 140, 167, 180, 189, 197, 199, 200, 234.

[5]References 14, 15, 17, 20, 21, 22, 23, 46, 47, 52, 53, 56, 57, 62, 64, 67, 69, 73, 74, 75, 83, 85, 88, 89, 92, 108, 111, 115, 117, 123, 126, 128, 129, 132, 139, 140, 142, 154, 155, 156, 162, 163, 165, 167, 170, 179, 186, 198, 199, 201, 202, 203, 205, 209, 210, 212, 215, 221, 241, 242.

(47 per cent) were classified as presumptive on the bases of clinical histories, descriptions of the lesions, photographs, biopsy studies, or positive smears.[6] In 104 cases the descriptions were too brief to permit inclusion among the proved or presumptive cases.[7] Cases reported as blastomycosis, which were obviously due to fungi other than Gilchrist's organism, are not included in the statistical study.[8]

SOURCE OF INFECTION

Evans (75) described the only proved case of direct transmission of blastomycosis from man to man. His patient was a physician who received a puncture wound on his finger while performing a necropsy on a case of systemic blastomycosis. A primary infection developed at the site of the needle puncture and *Blastomyces dermatitidis* was demonstrated

TABLE 1

Classification of cases reviewed

	SYSTEMIC	QUESTIONABLY SYSTEMIC	CUTANEOUS	TOTAL
Proved cases	60	4	16	80
Presumptive cases	57	13	93	163
Inadequately described cases	20	16	68	104
Total	137	33	177	347

four months later by biopsy and culture. Morris (168) also reported a blastomycotic infection in a physician who was doing necropsies and dissection in Chicago about the time this disease was being studied in this city. The patient developed a pustule on the left index finger but no statement was made concerning any direct contact with a case of blastomycosis. The acute illness began with respiratory symptoms and the infection terminated fatally. Braafladt (24) described a lesion on

[6] References 5, 6, 8, 12, 24, 26, 28, 29, 34, 39, 40, 41, 42, 49, 50, 51, 54, 57, 62, 65, 70, 71, 78, 79, 80, 81, 82, 91, 93, 94, 97, 100, 101, 104, 105, 109, 110, 112, 113, 114, 116, 118, 120, 121, 124, 125, 127, 130, 131, 134, 135, 138, 141, 143, 144, 145, 151, 153, 157, 158, 161, 163, 164, 165, 169, 176, 178, 181, 182, 191, 193, 196, 203, 208, 210, 213, 214, 216, 218, 220, 224, 227, 230, 231, 232, 233, 235, 236, 237, 238, 239, 247, 248.

[7] References 1, 3, 7, 9, 19, 24, 27, 28, 31, 38, 39, 45, 48, 57, 59, 61, 72, 76, 77, 82, 94, 98, 100, 101, 102, 103, 107, 118, 121, 122, 124, 130, 133, 136, 149, 150, 152, 157, 158, 161, 168, 171, 172, 173, 175, 177, 183, 185, 187, 192, 194, 196, 206, 207, 210, 217, 219, 222, 223, 226, 229, 243, 245, 246, 249.

[8] References 10, 25, 30, 84, 95, 96, 106, 184, 188, 228.

the breast of a Chinese woman who had nursed an infant with sores around its mouth. The breast was amputated and the patient was not seen again. Unfortunately the cultures were not sufficiently well described to be included among the proved or presumptive cases.

The high incidence of infection in the male sex suggests that the natural reservoir of the fungus is in nature. Stober's (225) theory that the natural habitat of the fungus is on damp rotting wood was supported by his isolation of a white mold from wood obtained from the dwelling place of one of the patients described in the Chicago series. This fungus was morphologically similar to *Blastomyces dermatitidis* and a vaccine prepared from this organism caused a reaction when injected into a patient with blastomycosis. This evidence suggested that the saprophytic mold was related to the pathogen, but the data presented do not justify drawing definite conclusions concerning the identity of the two fungi. Although most of the Chicago cases occurred in foreigners living in ill-lighted damp places, many infections in farmers and individuals not exposed to the unhygienic conditions described by Stober (225) have been reported. Several other observers (65, 69, 142) attached significance to the association of blastomycotic infections and exposure to working conditions such as excavation or working in dark cellars. Ravogli (195) suggested that the disease was contracted by individuals who handled dead animals and cited incidences of infection in hide workers, milkers, and stable employees (196). Werley (241), in one case, recorded the onset of the disease following the examination of an animal dead with gangrene, and Wohl (246) found a patient who was a stable worker. Other possibly significant observations are those of Toepel (230) who reported a case in which the initial lesion followed a thorn prick, and Crich (59) who described a patient with infection in the submaxillary gland after placing a piece of grass in his mouth. McKenty and Morgan (153) had a patient who associated the onset of his disease with a scratch on his face received while walking through the woods, and Robinson (203) described a man whose initial lesion followed walking through a field barefoot.

AGE INCIDENCE

The incidence of proved and presumptive cases in the various age groups may be seen in figure 1. Although patients infected with this fungus have been found in all decades of life, no systemic infections have

been described in a patient under the age of twelve years or over the age of seventy. Sixty-eight patients, or more than 50 per cent of those with systemic blastomycosis whose ages were reported, were between the ages of twenty and forty years. The age distribution is considerably wider in infections essentially limited to the skin. The youngest patient with proved blastomycosis was reported by Rosenthal (205) in an infant six

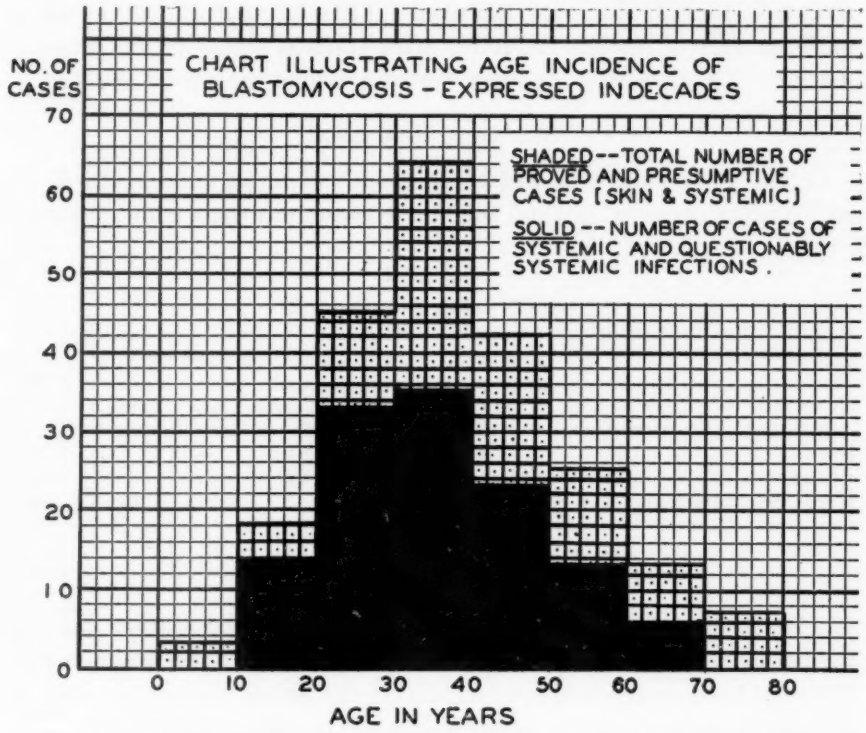

FIG. 1. Age incidence of proved and presumptive blastomycosis. Solid areas represent systemic and questionably systemic cases, the shaded areas representing total cases (systemic and cutaneous).

months of age. Varncy (232) described a case of skin infection in a nineteen year old girl whose initial lesion was said to have followed a minor injury at the age of six months.

SEX DISTRIBUTION

Males are much more frequently infected with *Blastomyces dermatitidis* than are females, the ratio being approximately 9 to 1 (see table 2).

Including only the proved and presumptive cases, 92 per cent of the patients with systemic and questionably systemic infections and 80 per cent of patients with skin or localized lesions were males.

RACIAL DISTRIBUTION

Of the 181 cases in which race was recorded, 50 (28 per cent) were Negroes and 131 (72 per cent) were white. The 3 Mongolian cases reported (24, 222, 231) were unproved. Fifty-four per cent of the white patients were of foreign extraction with Italians and Germans predominating. The disease is far more common among the poorer classes.

SEASONAL INCIDENCE

Of the 84 instances in which the month of onset was recorded, 10 patients (12 per cent) noticed the first symptom in the summer months,

TABLE 2

Sex distribution of blastomycosis

	SYSTEMIC		QUESTIONABLY SYSTEMIC		CUTANEOUS		TOTAL
	Male	Female	Male	Female	Male	Female	
Proved	57	3	4	0	12	3	79
Presumptive	51	6	10	2	72	18	159
Inadequately described	16	4	13	2	51	10	96
Total	124	13	27	4	135	31	334

16 (19 per cent) in the spring, 25 (30 per cent) in the autumn, and 33 (39 per cent) in the winter. These data, however, are of little significance since we have no information bearing on the actual time of entrance of the parasite into the body or the length of the incubation period.

GEOGRAPHIC DISTRIBUTION

Gilchrist's disease is an infection essentially limited to North America. Proved and presumptive cases have been found in twenty-eight states, and if one accepts the inadequately described cases this number is brought up to thirty (figure 2). There is an impression among some clinicians that the disease is rarely seen outside of California and Illinois (70), but in fact only 20 per cent of the recorded cases have been from Illinois (hence the name "Chicago disease"), and more cases of blastomycosis have been found in nineteen other states than have been reported

from California. Further evidence for the wide-spread distribution of the disease is obtained from discussions following papers on this subject. Willmot (244) in Kentucky states that he had seen 25 or 30 cases; Wende (240) observed 25 cases around Buffalo, New York, and Crutchfield (60), of Texas, remarked that the disease was very common along the Gulf states.

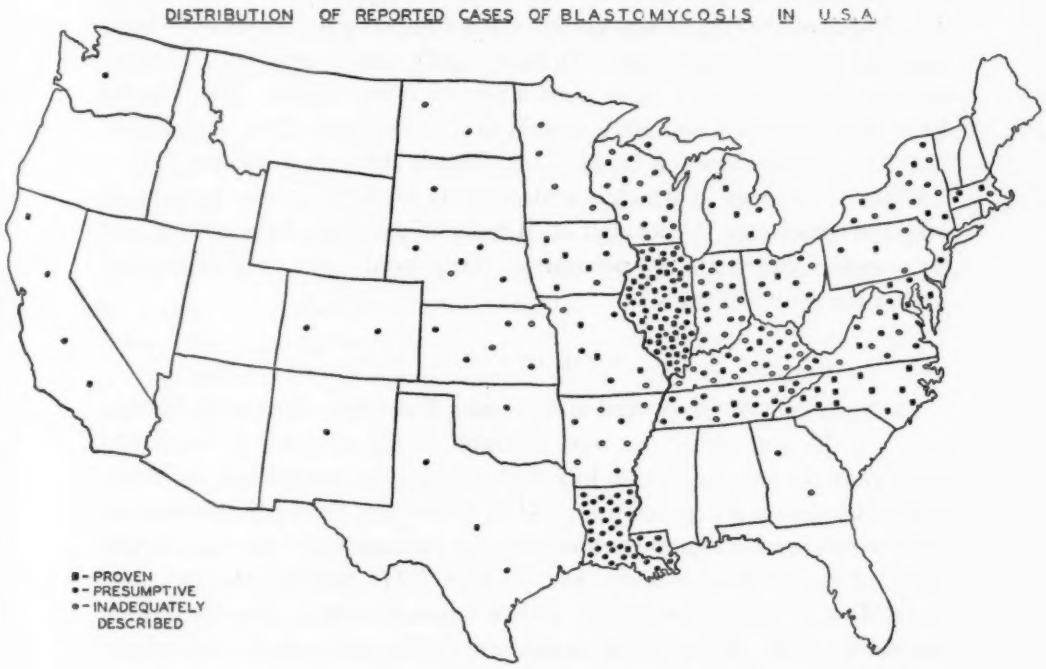

FIG. 2. Distribution of reported cases of blastomycosis in the United States. Solid squares = proved cases; solid circles = presumptive cases; open circles = inadequately described cases.

Analysis of the foreign cases is complicated by the failure to distinguish clearly between the American type of the disease caused by the mold-like *Blastomyces dermatitidis* and the European type caused by the yeast-like *Cryptococcus*. The South American workers give the name "blastomycosis" to many fungus infections, Almeida (4), for example, listing 108 different fungi as causing the disease. We have made no attempt to single out examples of Gilchrist's disease from the numerous case records reported from South America. We have found only two proved cases

originating outside this country, one of which was described in Canada by Shepherd and Rhea (215) and the other in England by Dowling and Elsworthy (69). McKenty and Morgan (153) reported four Canadian cases, one of which was fatal, but since no description of the organism was given, other than the statement that it was "definitely mycelial," these patients must be placed among the presumptive group. Another Canadian case was described by Gillies (91) with positive cultures but no description of the fungus was given. Other presumptive cases have been reported from the Philippines (8), Egypt (42), and Russia (97). Inadequately described cases have been reported from Canada (59), Puerto Rico (107), Costa Rica (206), Russia (133), England (226), China (24, 222, 231), South America (1, 61, 223), France (187), and Mexico (48).

Of the 340 cases in which a statement is made as to the locality of origin of the disease, 92 per cent of all cases, 95 per cent of the proved and presumptive cases, and 98 per cent of the proved cases have originated within the United States.

MODE OF ONSET

In 50 per cent of the proved and presumptive cases of systemic blastomycosis, the first symptoms were referable to the respiratory tract. In 4 per cent the primary lesion followed an injury of some kind, in 19 per cent a skin lesion was noted first, and in 23 per cent the earliest symptom was a subcutaneous nodule or abscess. In one case (143) the disease was initiated by chills and fever, and Keith's (121) patient had an onset resembling acute rheumatism. Other unusual initial symptoms were toothache (166), difficulty in swallowing (233), and pain in the epigastrium (120).

The respiratory signs and symptoms associated with the onset of the systemic form of the disease frequently resemble those of a cold or influenza which persist and are accompanied by weakness and loss of weight. The most frequent symptoms are cough, pain in the chest, and weakness. Haemoptysis occurred as an early symptom in 7 patients in whom the onset was primarily respiratory. Productive sputum occurs but is not common early in the disease. Other symptoms which have been described are tonsillitis, fever, bronchitis, dyspnoea, night sweats and pleurisy.

Swelling in the back, usually in the lumbar region, occurred in 6 patients, but in the remaining cases, in which a subcutaneous nodule or

abscess was the first sign, the sites of the original lesion were found to be so variable that the evidence strongly supports the theory that the portal of entry was the lungs and the nodules resulted from dissemination of the fungi through the blood-stream. In contrast to the cutaneous type of the disease which usually originates on some exposed part of the body, the abscesses seen in the systemic form of the disease occur most frequently on unexposed parts, such as the back, abdomen, thigh, etc. Evidences of pulmonary infection should be searched for in all patients with subcutaneous nodules or abscesses in which blastomycetes are found.

In patients with skin blastomycosis, the initial lesions are usually described as pimples or pustules which occur most frequently on some exposed part of the body or in an area which has been injured by scraping or other usually insignificant traumata. Hyde and Ricketts (113) described a man whose lesion followed a carbuncle on the face after the skin had been severely chilled. McKee's (151) patient developed a lesion after the cutting of a pimple while shaving, and Wood's (248) patient associated the onset of his infection with a stye in the left lower lid. Deafness was described as the first symptom in one of our patients (case 7).[9]

DISTRIBUTION OF LESIONS

Skin: In systemic blastomycosis the skin lesions are usually multiple and widely disseminated which is in contrast to that seen in the typical cutaneous type of the disease. The lesions in the latter form are more commonly single and spread slowly and peripherally. Very extensive involvement of the skin without evidences of infection of the internal organs also can occur (case 9). The face is most often involved, having been infected in 49 of the 109 proved and presumptive cases,[10] the lesions occurring most frequently on the cheek, eyelids and nose. Infections in the regions of the forehead, ears, lips, jaw and chin also have been described. The hands or wrists were involved in 27 instances,[11] the lesions being found most commonly on the dorsal surfaces. The

[9]Case reports referred to will appear in part II of this article in the April issue of the REVIEW.

[10]References 12, 41, 49, 62, 64, 71, 78, 80, 82, 89, 94, 97, 100, 113, 116, 123, 151, 153, 161, 169, 176, 196, 201, 218, 242, 246, 248. Case 9.

[11]References 26, 39, 62, 71, 89, 100, 112, 124, 127, 138, 142, 157, 158, 164, 167, 181, 182, 201, 203, 232, 239.

arms were infected in 22 cases,[12] most of the infected areas occurring on the forearms. Lesions in the region of the shoulder were described in 2 cases as were the areas around the elbows. The lower extremities were infected in 20 patients,[13] usually in the region of the foreleg or ankle. The scalp or neck were involved in 9 instances,[14] the genito-rectal region in 6,[15] and the thigh in 3 instances.[16] The skin over the thorax rarely is the site of a primary lesion. Fowler (81) described a sinus over the breast following a subcutaneous nodule in the mammary gland. Two of the patients reported by D'Aunoy and Bevan (62) had lesions on the chest. We have found no description of a primary skin lesion on the abdomen.

Histologically the lesions are similar to those found in verrucous tuberculosis, the rete showing extensive hyperplasia. Numerous miliary abscesses containing polymorphonuclear cells and cellular debris are seen, as well as occasional giant cells. In the corium is found the usual picture of subacute and chronic inflammation. The subcutaneous lesions are those of chronic or walled-off abscess formation.

Lungs: The lungs were found to be more frequently involved than any other of the internal organs of the body. Of the 60 cases of proved systemic blastomycosis, lung lesions were demonstrated by necropsy in 37,[17] and infection of the lungs was suspected or diagnosed clinically in 12 additional cases.[18] Of the 56 presumptive cases, lung infections were found by autopsy in 28 cases,[19] and a clinical diagnosis was made in 16 patients.[20] Of 41 necropsied cases of proved systemic blastomycosis there were only 4 instances in which the blastomycetes could not be found in this organ. Gaspar, *et al.* (85) found old fibrotic lesions in one necropsy, but the clinical course of the patient, the occasional blood-streaked sputum, and the roentgenographic shadow which gradually cleared up, led the authors to believe that the lungs had been

[12]References 23, 34, 41, 62, 64, 70, 82, 97, 113, 118, 124, 127, 141, 161, 167, 178, 214. Case 9.

[13]References 28, 49, 62, 97, 100, 104, 111, 112, 125, 141, 157, 158, 167. Case 9.

[14]References 34, 49, 62, 64, 70, 81, 97, 123, 201.

[15]References 89, 100, 153, 161, 201.

[16]References 89, 124, 157.

[17]References 14, 15, 21, 47, 52, 56, 57, 62, 67, 73, 74, 92, 108, 115, 126, 128, 132, 139, 140, 154, 156, 162, 170, 179, 198, 202, 210, 212, 215, 221. Cases 1, 2, 3, 4, 6.

[18]References 22, 46, 117, 142, 163, 186. Cases 5, 8, 10, 11.

[19]References 41, 50, 57, 62, 79, 93, 94, 101, 109, 110, 143, 144, 153, 163, 235, 236, 238.

[20]References 5, 24, 51, 54, 62, 65, 91, 101, 105, 163, 193, 208, 213, 233.

infected earlier in the disease. One of Ryerson's (209) patients was necropsied and described as having the lesions of generalized blastomycosis. Although the lungs were not mentioned specifically, the symptoms of pain in the chest and dyspnoea suggest that this case should be included with the cases of pulmonary infection. Montgomery (165), however, could not demonstrate the fungi in lung sections, and Rewbridge, *et al.* (199), who described a case of blastomycotic meningitis in a patient with tuberculosis, found only acid-fast bacilli in the pulmonary tubercles found at necropsy. To summarize, the lungs were probably infected in 39 (95 per cent) of the cases proved by autopsy.

The pathological picture of blastomycosis of the lung is quite variable. The lesion may be that of diffuse or focal consolidation, it may simulate the picture of miliary tuberculosis, or there may be larger nodules or abscesses distributed through the organ. Cavity formation occurs, but this type of lesion usually is small, rarely exceeding 1 cm. in size. Caseation occurs frequently in small focal areas. There has been some discussion as to differences in microscopical appearance of pulmonary lesions caused by *M. tuberculosis* amd *B. dermatitidis*, but Miller (159, 160) and Medlar (154) report that the finding of the organism is the only method of differentiating the infections. However, pathologists familiar with the microscopical appearance of the blastomycotic lesions frequently suspect the diagnosis and make an intensive search for the fungus.

Heart: The heart was involved in 9 instances, lesions having been found in the pericardium, myocardium and endocardium.[21] The mode of spread has been discussed by Baker and Brian (11) who concluded from an anatomical study of 2 patients in our series (cases 3 and 6) that the pericardial lesions were the source of the pulmonary blastomycotic nodules. They believe, however, that it is possible for the cardiac lesions to develop by means of a retrograde lymphatic extension.

Skeletal system: The bones and joints were infected in 50 per cent of proved and presumptive cases. Of the 59 proved cases of systemic infection, 31 patients had bone or joint lesions at autopsy, and in 4 instances a clinical diagnosis was made, making a total of 35 (60 per cent) of proved cases showing infection of these tissues. The pathological picture in general is one of destruction, that is, abscess formation and erosion. Osseous lesions occur most commonly in the vertebrae (24 in-

[21]References 50, 57, 62, 109, 110, 128, 154, 235. Cases 3, 6.

stances),[22] and result occasionally in formation of psoas abscesses (14, 57, 74) (case 1). In our series (case 10) a partial collapse of the twelfth thoracic vertebra was thought to be caused by blastomycotic invasion. The ribs are next most frequently infected (14 instances),[23] often by direct extension from the lungs. The bones of the skull were involved in 9 cases.[24] Other bones reported to have been involved are the sacrum, tibia, fibula, clavicle, iliac, humerus, ulna, and the small bones of the feet, ankles, hands, and wrists. In 7 instances the knee joint was involved,[25] and in 6 patients the elbow joint was infected.[26]

The spleen was involved in 24 cases,[27] as was *the liver*.[28] *The pancreas* was infected in 4 instances.[29] The lesions in these organs are usually nodular or miliary in type but rarely occur in large numbers. In one of our patients (case 4) the liver lesion was granulomatous in nature. Toepel (230) reports fibrous patches in the liver, but these were not proved to be of blastomycotic origin.

The kidneys were involved in 22 cases, 16 of which were proved to be blastomycotic.[30] The lesions are usually nodular or miliary in type, but the occurrence of small abscesses has been described.

The gastrointestinal tract is only occasionally the site of a lesion. Eisendrath and Ormsby (73) described a nodule in the colon which did not contain organisms. A nodule in the stomach, 7 cm. in diameter, has been reported (215). Among the presumptive cases Vinson, *et al.* (233) described an oesophageal mass, and Shields (216) reported a patient in whom were found lesions of the rectum and anus. The oesophagus was involved in one of our patients (case 2).

Infection of *the peritoneum* has been reported rarely (57, 215); one of the patients in our series (case 10) had a nodular peritonitis. The details of the operative findings in this patient have already been described (99).

[22]References 14, 52, 56, 57, 67, 73, 74, 85, 92, 108, 114, 115, 120, 126, 144, 154, 163, 202, 210, 213, 235. Case 1.

[23]References 47, 57, 62, 74, 110, 114, 126, 153, 170, 235. Cases 3, 6.

[24]References 15, 47, 85, 110, 114, 153, 210, 235.

[25]References 47, 126, 132, 163, 170, 212. Case 2.

[26]References 47, 56, 110, 143, 196, 215.

[27]References 15, 21, 50, 57, 62, 79, 109, 110, 115, 126, 128, 154, 170, 179, 198, 202, 212, 215, 235, 236. Case 2.

[28]References 15, 21, 50, 62, 79, 101, 128, 139, 170, 179, 198, 202, 215, 235, 236. Cases 2, 4, 6.

[29]References 128, 139, 170, 235.

[30]References 15, 47, 57, 67, 73, 108, 126, 128, 154, 170, 179, 198, 215. Case 4.

The adrenals have been invaded in 2 cases of proved blastomycosis (15, 215) and in one case presumably blastomycotic (50). *The thyroid* gland was involved in only 1 case (156), and invasion of the thyroid cartilage has been described (115).

Lesions of *the prostate* have been reported in 11 patients,[31] *testis* in 4 cases,[32] *epididymis* in 3 cases,[33] and *the seminal vesicles* in 2 patients.[34] The first description of invasion of *the uterus* and *tubes* by *Blastomyces dermatitidis* was reported from this hospital (99) and is included in the present series (case 10).

Blastomycotic lesions of *the central nervous system* have been found in 16 cases.[35] The usual picture is that of single or multiple small abscesses in the cerebellum, cerebrum or brain stem. Riley and LeCount (202) reported a case with a basilar purulent meningitis, and MacBryde and Thompson (140) found blastomycetes in a patient with cloudy spinal fluid. An extradural abscess was described by Gaspar, *et al.* (85), and Rewbridge, *et al.* (199) described a case of blastomycotic meningitis in a patient who had none of the other organs involved. In one of our patients (case 1) a basilar meningitis was found at autopsy. Of the presumptive cases, meningitis has been described by Hurley (110) and McKenty and Morgan (153), and a clinical diagnosis of myelitis was made by Wade and Bel (235) in one of their patients who died but was not necropsied.

Other unusual sites of infection are *the eye* (47, 212) and *larynx* (108). Among the presumptive cases we find a description of infection of the larynx and vocal cords (65) and a history of a patient with retropharyngeal abscesses (196).

In summary, the organs of predilection of the fungus *Blastomyces dermatitidis* are the skin and subcutaneous tissues, lungs, bones, joints and less commonly the central nervous system. Infection of the abdominal organs occurs frequently, but the lesions usually are not sufficiently extensive to be of any pathological significance.

SERUM ANTIBODIES

Since 1933 we have carried out complement fixation reactions with sera obtained from all our patients. The technique has been described

[31]References 15, 47, 56, 126, 132, 186, 202, 210, 215. Case 3.
[32]References 67, 108, 117, 165.
[33]References 108, 144, 202. Case 3.
[34]Reference 186. Case 3.
[35]References 15, 62, 73, 85, 110, 126, 132, 140, 153, 166, 170, 199, 202, 235. Case 1.

by one of us (146) and utilizes as antigen a saline suspension of blood agar cultures of the living yeast-like organisms. The dose of antigen used for each series of tests is calculated by determining the anticomplementary titre of the freshly prepared suspension. The antigen prepared in this way has the disadvantage of having a comparatively weak combining titre and necessitates using a freshly prepared antigen for each test. This does not make possible accurate comparisons of antibody content. However, we have never obtained a falsely positive reaction on at least 100 sera from patients who did not have blastomycosis.

Our experience with the complement fixation reaction in blastomycosis indicates that the antibody titre in this disease is of importance in determining the degree of infection. A high titre indicates extensive infection; a low titre or negative reaction in a patient with blastomycosis usually signifies that the disease is not wide-spread. Complement fixation tests were done on 10 of the 13 patients in our series, cases 1, 4 and 8 having been seen before serological studies were begun. Positive tests were obtained in 5 patients (cases 2, 3, 5, 6 and 10). All except one (case 10) died. The antibody content of the serum of the surviving patient remained comparatively high from July, 1934 until February, 1935. On April 2, 1935 her uterus and tubes were removed (99). A serological test on April 10 showed a slight decrease in antibody titre, and several tests since December, 1935 have been entirely negative.

Patients 7, 9, 11, 12 and 13 had negative serological reactions. Four of these patients (cases 7, 9, 12 and 13) had infections limited essentially to the skin, although it was very extensive in one (case 9). One patient (case 11) had a large pulmonary X-ray shadow in addition to six subcutaneous abscesses. He recovered after treatment which included desensitizing doses of *Blastomyces* vaccine. Repeated complement fixation tests were negative, showing that these small doses were not sufficient to stimulate detectable antibody production.

In addition to utilizing the antibody content of the serum as an index of the extent of the infection, the complement fixation reaction has been of value in demonstrating the homogenicity of the antigenic structure of the fungi isolated from our cases. The serum from one of our patients (case 2) also fixed complement with cultures of *Glenospora Gammeli, Endomyces capsulatus, Monosporium tulanense* amd *Blastomycoides tulanense*, all of which are morphologically similar to *Blastomyces dermatitidis* and considered by our group to be synonomous (55).

THE ALLERGIC STATE

The similarity of many of the pathological and clinical features of blastomycosis to tuberculosis suggests that a type of hypersensitiveness similar to that seen in tuberculosis would not be surprising. Although the term "allergic type of reaction" is occasionally encountered in descriptions of pathological lesions (156), investigations of this phenomenon have been few in number. Davis (63) failed to produce anaphylactic shock in infected guinea pigs with a saline extract of ground organisms. Long (137) succeeded in infecting guinea pigs with heavy suspensions of the fungus, and later injected a filtrate of a six weeks old broth culture into the testis, resulting in a pathological picture markedly similar to that seen when tuberculin is injected into the testis of allergic tuberculous animals. No skin sensitivity developed in these animals.

Stober (225) prepared a heat-killed vaccine from old glucose broth cultures by suspending the organisms in the filtrate and injected it in several patients (15, 22). The subcutaneous injection of the vaccine into blastomycotic patients resulted in elevations of temperature from 0.5° to 2.0°F. with local redness and pain. Large doses caused the formation of sterile abscesses. In nonblastomycotic patients sterile abscess formation resulted from injection of 4.0 cc. quantities of the material. Focal reactions such as sloughing of scabs and increased drainage occurred in the blastomycotic cases. These results suggested the possibility of using vaccines in therapy, but, as will be seen from our studies, their value appears to be due to the reduction of allergy by the injection of subreacting doses rather than in the use of doses large enough to produce focal reactions.

Boughton and Stober (22) found that the endodermal injection of vaccines from three strains of *Blastomyces* from other patients produced a papule lasting four days in their patient. Stein (223) observed a patient who developed a nodular type of skin infection while residing in Brazil and who was diagnosed blastomycosis by a Brazilian physician, but when seen in Vienna by Stein no cultures could be obtained. A suspension of a ground lymph node from the patient produced a positive skin reaction. Stein obtained a culture of *Blastomyces dermatitidis* from Doctor Gilchrist, and a delayed (24 hours) skin reaction resulted from injection of an extract of this organism. Garr (83), using a filtrate of a bouillon culture of the organism, obtained only a slight local reaction with doses as large as 1.0 cc. Maschkilleisson (148) reported positive

skin tests with a vaccine made from both the "white" and "rose" colored fungi isolated from each of his three patients. Castellani and Jacono (44) tested patients and controls with a tetravalent antigen prepared from six weeks old glycerine veal broth cultures of *Geotrichum immitis*, *G. dermatitidis*, *Monosporium tulanense* and *Glenospora lanugosum*. Skin tests were negative in 45 of 46 nonblastomycotic patients, and in 3 patients with blastomycosis, one positive, one negative and a weakly positive reaction were recorded.

In our series, skin tests were done by injecting intracutaneously 0.1 cc. of a heat-killed vaccine prepared by washing off the yeast-like growth on blood agar and diluting 1:1,000 by volume in sterile saline. Within fifteen to twenty minutes after the injection of this material, a punctate erythema appears around the injected area, but this reaction is not specific as it has been occasionally observed in patients with nonblastomycotic infections. The specific reaction is very similar to a positive tuberculin reaction, appearing within 12 to 24 hours and reaching a maximum in two to four days. The reaction may proceed to sterile abscess formation in very allergic patients.

A state of anergy, probably analogous to that seen in tuberculosis, is seen in patients in the terminal stages of the disease. Cases 2 and 8 illustrate the anergic state in which a negative skin reaction occurs in patients overwhelmed by the infection. Patient 3, who also gave a very weak reaction, succumbed. Two patients (cases 7 and 9) failed to react to the injection of this material although death was not imminent. Unfortunately one patient (case 7) could not be followed. The other patient (case 9) presented extraordinarily extensive skin involvement, and an allergic reaction to an intracutaneous injection could hardly be expected although it is difficult to understand why the antibodies should not have been found in a patient with such a wide-spread infection.

Varying degrees of allergy were present in cases 10, 11, 12 and 13, sterile abscesses being produced in all but case 10. A considerable degree of desensitization was accomplished in all these cases. In none did the skin tests become entirely negative, but abscess formation was abolished and the areas of erythema were considerably reduced.

The Department of Chemistry, Duke University, has been coöperating with our group by analyzing the chemical constituents of the fungus. Preliminary experiments with the carbohydrate and protein fractions of *Blastomyces dermatitidis* have shown that the reaction to the carbohydrate reaches a maximum in twenty-four hours and the protein causes

a delayed reaction (cases 12 and 13). Partial desensitization was accomplished in one patient (case 13) by intravenous injection of the purified carbohydrate fraction. However, we have not had enough experience with the chemical fractions to make comparisons of the skin testing and desensitizing properties of the various fractions with the whole heat-killed vaccine.

DIAGNOSIS

The diagnosis can be proved unequivocably only by the isolation and identification of the infecting organism, *Blastomyces dermatitidis*. However, from the history and clinical appearance of the infection, direct examination of material from the lesions, skin tests, and complement fixation reactions, tentative diagnoses can be made which should stimulate efforts toward isolation of the fungus.

The usual history of the skin type of blastomycosis is that a papule or small pustule has appeared on some exposed part of the body and has spread peripherally very slowly, frequently becoming crusted. The clinical appearance varies greatly with the size and age of the lesion, but the following characteristics generally are found: a crusted wart-like process which bleeds very easily and has a definite raised border honeycombed with minute abscesses containing thick glary or mucoid pus in which are found the double-contoured budding cells.

The systemic form of the disease in about one-half of the cases begins as an upper respiratory infection which becomes chronic and is followed by the appearance of subcutaneous abscesses or skin lesions from which the fungus can be grown. Roentgenological examination frequently is helpful in the diagnosis of pulmonary infection early in the disease. A dense irregular shadow extending from the hilum toward the periphery is most characteristic of blastomycosis. Potter (190) published an excellent description of the roentgenological appearance of blastomycosis of the lungs, and the shadows found in our patients showed the same characteristics. Isolation of the fungus from the sputum is not difficult if sufficient material can be obtained.

In pulmonary infections of obscure aetiology in which blastomycosis is suspected, a skin test and complement fixation reaction should be done. A delayed tuberculin-like reaction is highly significant as is fixation of complement with the *Blastomyces* antigen.

The procedures necessary for isolation and identification of *Blastomyces dermatitidis* have already been described (147) and can be summarized

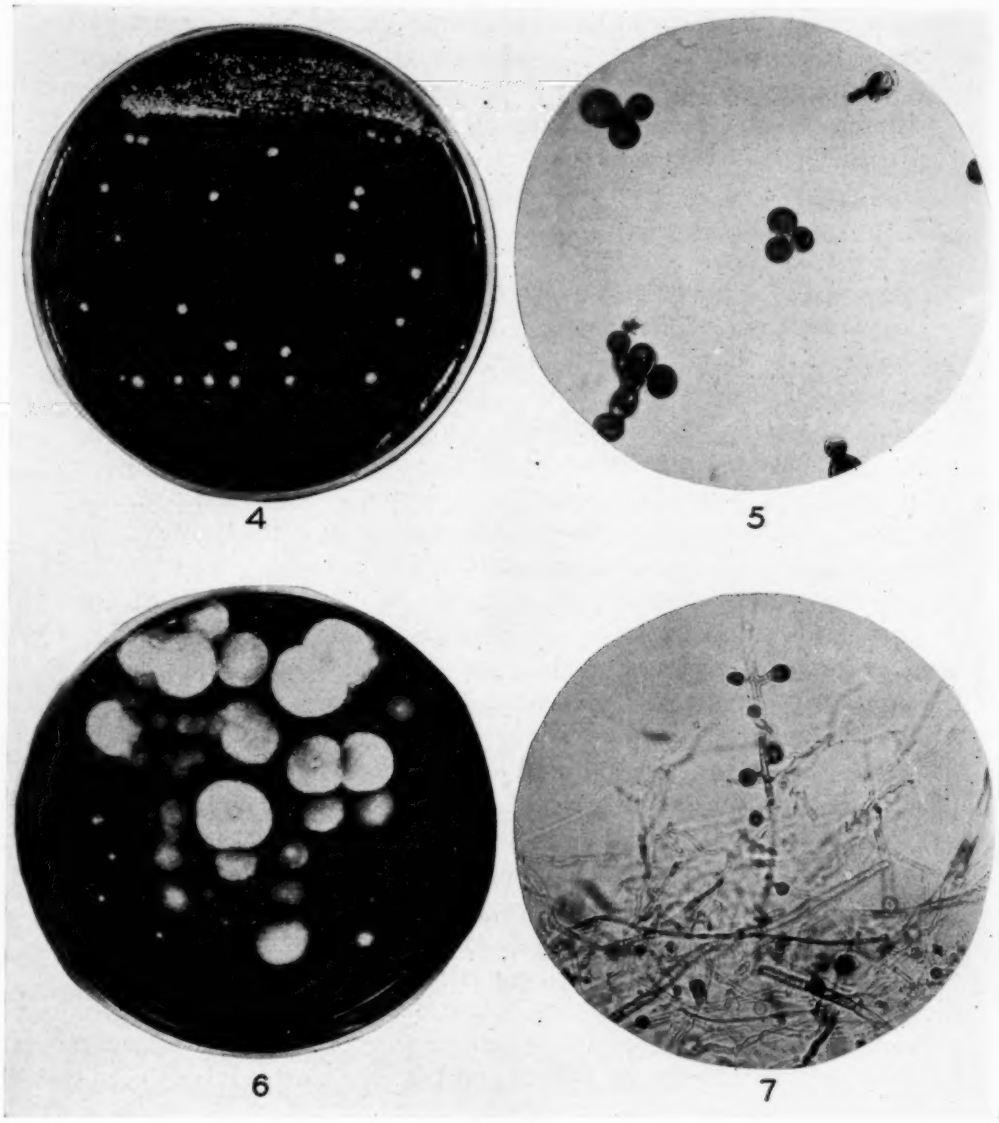

PLATE 1

Macroscopic and microscopic characteristics of cultures of *Blastomyces dermatitidis*

FIG. 4. Crinkled, waxy colonies grown on blood agar at 37°C. for 7 days.

FIG. 5. Microscopic appearance of smear (high dry lens) made from plate shown in fig. 4. Stained with tincture of iodine.

FIG. 6. Mold-like appearance of fungus cultivated for eleven days on Sabouraud's medium at room temperature.

FIG. 7. Microscopic appearance of fungus in mold-like stage, showing long mycelial threads and lateral conidia. Stained with lactophenol and cotton blue.

as follows: The material should be streaked heavily on blood agar plates and Sabouraud's slants. Incubation should be carried out at room temperature and at 37°C. The cultures should not be discarded for two or three weeks since colonies of *Blastomyces* may not appear for two weeks. The organism on blood agar at 37°C. grows as a small, wrinkled, waxy colony not dissimilar from a colony of tubercle bacilli (plate 1, figure 4). Microscopically it consists of large, rounded, thick-walled cells, many of them budding and some showing rudimentary hyphae (plate 1, figure 5). On Sabouraud's medium at room temperature the fungus grows as a white mold with an abundant aerial mycelium (plate 1, figure 6). Microscopically numerous branched hyphae with lateral conidia and thick swollen chlamydospores may be seen (plate 1, figure 7). If transplants of the mold-like growth on Sabouraud's medium are made to blood agar at 37°C., the fungus again reverts to the crinkly, waxy yeast-like colonies described above. Mold-like colonies can be obtained by transplanting the waxy colonies to Sabouraud's medium and incubating at room temperature.

PROGNOSIS

Systemic infection with *Blastomyces dermatitidis* is highly fatal, reaching a mortality much higher than that of tuberculosis. Of the 59 proved cases of the generalized disease, 49 were fatal within five years. Of the 57 presumptive cases, 40 were known to be dead within the same period; one patient died six years after the onset of symptoms (208), and another died after approximately seven years of illness (236). The duration of illness in the fatal cases, dating from the time of onset of the first symptom, is given in table 3.

The mortality rate of all 117 reported systemic cases (proved and presumptive) is 78 per cent if the patients who were not followed are included, and 83 per cent if they are excluded. It is 92 per cent if those who had been followed for less than two years from the onset also are excluded.

Of the 8 patients in whom death was not reported and who were followed for at least two years from the onset of the disease, 2 are included in the present series (cases 10 and 11). Blankenhorn and Gammel (20) report their patient as apparently well as long as two years after treatment. Gilchrist's (88) patient had the disease for four years, and Parmenter and Simpson's (186) case showed no evidence of recurrence five years after the onset. Herrick (105) described a patient who

recovered after establishing a residence in California and was well three years after the onset. Braafladt's (24) patient showed considerable improvement four years after the initial symptoms. One of Hyde and Montgomery's patients described by Montgomery and Ormsby (163) was followed at irregular intervals for eight years, at which time the patient was definitely worse. Unfortunately this patient could not be located subsequently. Although 93 per cent of the patients who die do so within three years, evaluation of the effects of any treatment should be interpreted cautiously unless the patient is followed for a much longer time.

In the cutaneous type of blastomycosis, on the other hand, the first lesion, usually described as a pimple or pustule, may remain stationary for years before spreading. However, some lesions are diagnosed very

TABLE 3

Duration of disease in known fatal cases of systemic blastomycosis

	PROVED	PRESUMPTIVE	TOTAL
Died within 6 months	13	7	20
Died 6–12 months	22	10	32
Died 1–2 years	8	7	15
Died 2–3 years	4	1	5
Died after 3 years	2	3	5
Length of illness undetermined	0	14	14

early. Rosenthal (205), for example, observed an unusual case of an epidermal abscess in an infant which was of only three weeks' duration. The usual time interval from onset till diagnosis varied from three or four months to several years, but cases have been found in which the interval is a decade or more. Millard and Goddard (158) date back twenty years a single lesion on the hand of a seventy-year old farmer, and Varncy (232) describes a skin lesion on the hand of a nineteen-year old girl who ascribed the onset of the lesion to an injury received at the age of six months. In these long histories the question always arises as to the possibility of secondary infection with blastomycetes in a previously inflamed area.

TREATMENT

The high incidence of the disease in people of poor economic circumstances is strong evidence that general hygienic measures are of great importance in preventing infection and should be of value in treatment

after infection has been established. Since the prognosis differs so greatly, depending upon whether or not the infection is systemic or confined to the skin, the therapy of each type should be considered separately.

Cutaneous blastomycosis: Since Gilchrist (88) described the rapid healing of a large skin lesion and subcutaneous abscesses in a Negro after the administration of potassium iodide, this drug has been used extensively in the treatment of all forms (cutaneous and systemic) of this disease, usually with marked improvement in the majority of cases. Although doses up to 150 grains (10 g.) t.i.d. (242) usually do not produce iodism, many patients cannot tolerate this dosage. Langdon's (127) patient showed slight symptoms of iodism when 6 g. t.i.d. were given, but treatment at the level of 12 g. daily was continued without trouble. Sodium iodide has been given by mouth (71), but this drug has usually been given intravenously as a supplement to oral potassium iodide (80, 100, 157). Hamilton's (100) patient received doses as high as 4 g. intravenously. Iodides, however, occasionally fail (232), and Graves (94) reported that one of his patients did not improve with potassium iodide by mouth and local applications of tincture of iodine. Jackson (118) reported 2 cases which failed to heal with adequate doses of potassium iodide.

One of our patients with skin blastomycosis (case 12) illustrates the harmful effect of iodides when given to an individual who is allergic to the infecting fungus. A skin test with the standard heat-killed vaccine (diluted 1:1,000) resulted in the formation of a sterile abscess at the site of injection. Two weeks after iodide therapy was started, this patient, who was previously afebrile, began to have irregular fever reaching 39.6°C. (103°F.) (figure 3), and the tissues surrounding the lesions became liquefied, leading to a serious spread of the infected area. He also lost 3.3 kilograms in weight in one week. The fever disappeared after discontinuance of the drug, and desensitizing doses of vaccine were given. After partial desensitization was accomplished iodides were again administered, resulting in gradual but satisfactory healing of the lesions.

Salvarsan was combined with iodides by Ormsby (178) in 2 patients and resulted in healing of the lesions in one patient, but no improvement resulted in the other. Clarkson and Barker (49) reported a patient who had received antisyphilitic therapy with arsphenamine but showed no improvement in his blastomycotic lesion.

Among the local measures which have been used, usually combined with oral iodide therapy, are: iodide of lead ointment (71), silver nitrate (113), tincture of iodine (169), bichloride of mercury (138), 1 per cent copper sulphate (246), phenol (124) cauterization with a hot iron (118), and freezing with carbon dioxide snow (70).

Curettage of the lesions and X-ray therapy have been successfully used in a large number of cases. In view of the treatment to be dis-

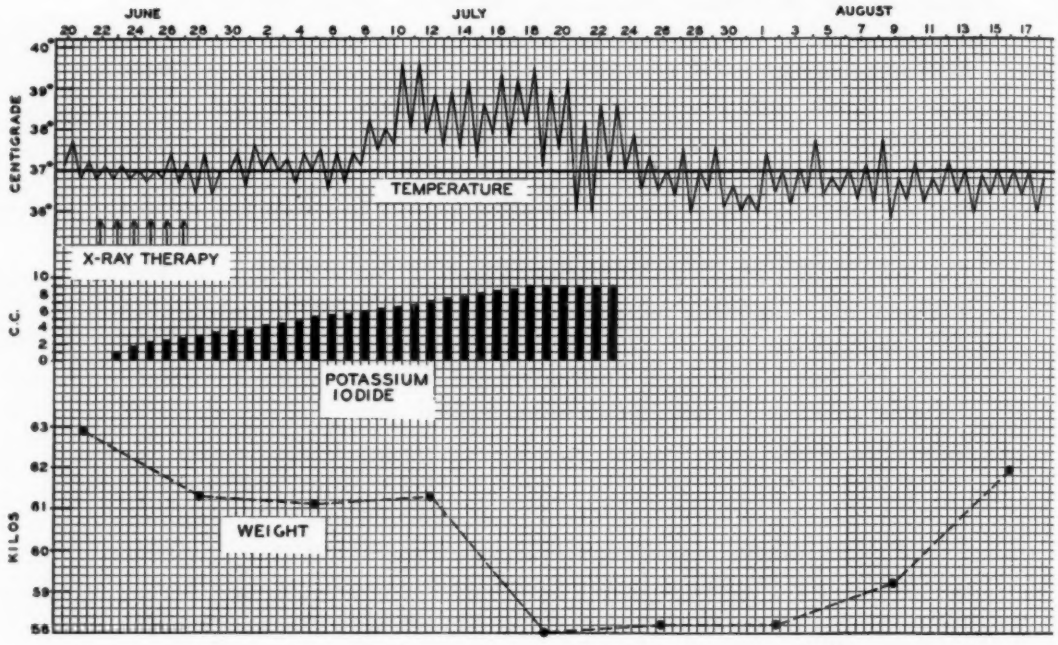

FIG. 3. Harmful effect of iodide administration in a very allergic individual (case 12). Shaded bars = dosage of potassium iodide (in cc. of saturated solution). Temperature curve, in degrees centigrade, highest and lowest temperature recorded for each day. Weight in kilograms.

cussed later, it is interesting to note that occasionally this form of therapy may cause local inflammation around the site of the lesion (78). Radium was used successfully by Simpson (218) and Forsberg and Stern (80).

Systemic blastomycosis: Potassium iodide has been used more extensively than any other drug in the treatment of the systemic form of the disease, but, as can be seen from the data on prognosis, the results are very discouraging. Desjardin (66) quotes Hyde and Ricketts as follows: "In no instance yet recorded has the continued administration of the

iodide of potassium conducted any single case to a satisfactory recovery." Of the cases reported, this drug usually has had no effect on the progress of the disease although in some patients temporary improvement has been described. Doses as high as 960 grains a day (60 g.) have failed to cause a remission (165), and some patients are definitely harmed. Montgomery's patient (162) became worse on a dosage of 10 g. t.i.d. and improved somewhat when the drug was stopped. Shepherd and Rhea (215) noticed that 1.2 g. of potassium iodide t.i.d. seemed to make the skin lesions worse, and signs of lung involvement appeared after treatment was begun. Intravenous sodium iodide (2 g.) caused chills and fever in Garr's (83) patient.

In our series, gradually increasing doses of potassium iodide were of no effect in cases 1, 2 and 3. In case 8 there was rapid improvement within two weeks after therapy was begun. Cases 4, 5 and 6 may be cited as examples to illustrate the harmful effects of the drug. One patient (case 4) had a pulmonary lesion which had remained stationary for about five years, and iodide therapy was followed by a rapid spread of the lung lesion and death. Case 5 improved slightly for two weeks but died in spite of vaccine and adequate doses of iodine. Case 6 improved clinically for several weeks, but the roentgenogram showed simultaneous spreading of the lung lesion and the outcome was fatal.

Intravenous arsenicals have been shown to be without effect on the progress of the disease (52, 83, 85), and Montgomery's patient (165) became worse after two injections of arsphenamine.

X-ray treatments have been attempted in a few of the systemic infections without any evidence of permanent improvement.

Herrick (105) observed an interesting case in a woman who had been treated with potassium iodide for some time with but slight improvement, but who went to California with "31" sores on her body and healed within six months after arrival.

Sanderson and Smith (211) observed the inhibiting effect of gentian-violet on *Blastomyces dermatitidis* and noted that the growth of the fungus in culture was inhibited by a 1:500,000 dilution of the dye. They believed that this therapy was worth a trial since a theoretical dilution of 1:200,000 could be obtained in the body.

Bergstrom, et al. (17) recently reported excellent results after administration of colloidal copper sulphate.

Vaccine therapy was used by Christensen and Hektoen (46) in 2

patients, one of whom responded to the first injection with a rise in leucocytes, but no effect on the white count or temperature could be noted after subsequent injections. The second case did not respond to this form of therapy. Boughton and Stober (22) reported promising results in their patient in which the injections caused a rise in temperature and an inflammatory reaction around the lesions. On the other hand, Hill and Dickson (108) and Garr (83) could observe no beneficial effect.

It is apparent from the few cases in the literature that the favorable result expected in vaccine therapy has been the production of focal or generalized reactions. In contrast to this we have tried to avoid such reactions by the injection of only subreacting doses. Using the skin test as a guide, dilutions as high as 1:1,000,000 (1:1,000 dilution of the original 1:1,000 skin testing material) were injected, beginning with 0.1 cc. of the diluted material and gradually increasing the dose every two or three days. In case of any slight local or general reaction, the quantity injected was decreased to the previous nonreacting dose. When the dosage of diluted vaccine reached 1.0 cc., increasing doses of a less dilute suspension were injected in the same manner. In this way it was possible, after four to eight weeks' therapy, to demonstrate a decrease in sensitivity as shown by skin test (cases 10, 11, 12 and 13). In none of these cases was a negative skin reaction obtained, but abscess formation to the skin testing material was abolished, and the area of erythema produced by the injection was greatly reduced. Iodides could then be safely administered to these patients. Healing of the pulmonary lesions under this form of treatment is well illustrated in cases 10 and 11.

As a result of our experience with this disease, we routinely skin-test our patients with the standardized *Blastomyces* vaccine before any form of therapy is considered. Iodides are given cautiously and only if the patient shows a negative or weakly positive skin reaction. Iodides are distinctly harmful if the patient is allergic. Our comparative morphological and serological studies of different strains of *Blastomyces dermatitidis* (55, 146, 147) indicate that these strains are antigenically homogeneous, and a stock strain maintained on blood agar can be used as a source of skin-testing material, complement fixing antigen and therapeutic vaccine.

The summary and conclusions drawn from the review of the literature and our experience with 13 cases of blastomycosis will be published at the end of the second part of this study.

BIBLIOGRAPHY

(1) ABERASTURY, M.: Bol. Inst. de med. exper. para el estud. y. trat. d. cáncer, 1926, *2*, 885.
(2) AGOSTINI, A.: J. Trop. Med. & Hyg., 1932, *35*, 266.
(3) ALBERS, A.: Tr. Chicago Path. Soc., 1907, *7*, 21.
(4) ALMEIDA, F.: Ann. Fac. de med. de São Paulo, 1933, *9*, 69.
(5) ALTSCHUL, F. J.: J. M. Soc. New Jersey, 1930, *27*, 132.
(6) ANDERSON, J. W.: Virginia M. Monthly, 1921, *48*, 475.
(7) ANTHONY, H. G., AND HERZOG, M.: J. Cutan. & G. U. Dis., 1900, *18*, 1.
(8) ASHBURN, P. M., AND CRAIG, C. F.: Mil. Surgeon, 1907, *21*, 45.
(9) AUSTIN, M. A.: J. Indiana M. A., 1911, *4*, 436.
(10) AVERY, J. F.: Journal Lancet, 1931, *51*, 289.
(11) BAKER, R. D., AND BRIAN, E. W.: Am. J. Path., 1937, *13*, 139.
(12) BALDWIN, L. B.: J. A. M. A., 1900, *34*, 292.
(13) BASGAL, W.: Contribuicao ao estudo das blastomycoses pulmonares, 1931, Thesis Instituto Oswaldo Cruz, Rio de Janeiro.
(14) BASSOE, P.: J. Infect Dis., 1906, *3*, 91.
(15) BECHTEL, R. E., AND LE COUNT, E. R.: Arch. Int. Med., 1914, *13*, 609.
(16) BENHAM, R. W.: Arch. Dermat. & Syph., 1934, *30*, 385.
(17) BERGSTROM, V. W., NUGENT, G., AND SNIDER, M. C.: Ibid., 1937, *36*, 70.
(18) BEURMANN, L., AND GOUGEROT, H.: Les nouvelles mycoses, 1912, Masson et Cie, p. 34.
(19) BEVAN, A. D.: J. A. M. A., 1905, *45*, 1492.
(20) BLANKENHORN, M. A., AND GAMMEL, J. A.: J. Clin. Investigation, 1927, *4*, 471.
(21) BOUGHTON, T. H., AND CLARK, S. N.: Arch. Int. Med., 1914, *13*, 594.
(22) BOUGHTON, T. H., AND STOBER, A. M.: Ibid., 1914, *13*, 599.
(23) BOWEN, J. T., AND WOLBACH, S. B.: Jour. Med. Res., 1906, *15*, 167.
(24) BRAAFLADT, L. H.: China M. J., 1921, *35*, 30.
(25) BRANDWEINER, A.: Arch. f. Dermat. u. Syph., 1904, *71*, 49.
(26) BRAYTON, A. W.: Indiana M. J., 1900, *18*, 403.
(27) BRAYTON, A. W.: Quoted by AUSTIN (9).
(28) BRAYTON, A. W.: Tr. Indiana M. A., 1907, p. 35.
(29) BRAYTON, J. R.: Med. Arts & Indianapolis M. J., 1931, *34*, 706.
(30) BREWER, G. E., AND WOOD, F. C.: Ann. Surg., 1908, *48*, 889.
(31) BROOKSHER, W. R.: South. M. J., 1932, *25*, 412.
(32) BRUMPT: Precis de Paras., 1910, ed. 1, p. 718.
(33) BRUMPT: Precis de Paras., 1913, ed. 2, p. 934.
(34) BURKHEAD, C. R.: J. Kansas M. Soc., 1922, *22*, 101.
(35) BUSCHKE, A., AND BUSSE, O.: Vereins-beilage der Deutsche med. Wchnschr., 1895, p. 14.
(36) BUSSE, O.: Centralbl. f. Bakt., Abt. I, 1894, *16*, 175.
(37) BUSSE, O.: Arch. f. path. Anat. u. Phys., 1895, *140*, 23.
(38) CAMPBELL, J. L.: Atlanta J. Rec. Med., 1909, *12*, 308.
(39) CARTER, R. M.: J. Indust. Hyg., 1923–24, *5*, 457.
(40) CASTELLANI, A.: Proc. Roy. Soc. Med., 1928, *21*, part 1, 447.
(41) CASTELLANI, A.: Am. J. Trop. Med., 1928, *8*, 379.
(42) CASTELLANI, A.: New Orleans M. & S. J., 1928, *81*, 260.
(43) CASTELLANI, A.: Amer. Med., 1928, *23*, 289.
(44) CASTELLANI, A., AND JACONO, I.: J. Trop. Med., 1933, *36*, 297.
(45) CHILDREY, J. H., AND NEW, G. B.: Arch. Otolaryng., 1930, *12*, 184.
(46) CHRISTENSEN, C., AND HEKTOEN, L.: J. A. M. A., 1906, *47*, 247.
(47) CHURCHILL, T., AND STOBER, A. M.: Arch. Int. Med., 1914, *13*, 568.

(48) CICERO, R. E.: Gac. méd. de Mexico, 1928, *59*, 565.
(49) CLARKSON, W., AND BARKER, A.: Virginia M. Monthly, 1933, *60*, 83.
(50) CLEARY, J. H.: Medicine (Detroit), 1904, *10*, 818.
(51) COATES, W. E.: Ibid., 1900, *6*, 100.
(52) COLE, W. H.: Ann. Surg., 1924, *80*, 124.
(53) COLEY, W. B., AND TRACY, M.: J. Med. Res., 1907, *16*, 237.
(54) COMPTON, B. S.: U. S. Vet. Bur. M. Bull., 1929, *5*, 299.
(55) CONANT, N. F., AND MARTIN, D. S.: (To be published).
(56) COOPER, C. N.: J. Iowa M. Soc., 1931, *21*, 119.
(57) COUPAL, J. F.: Internat. Clin., 1924, 34th Series, vol. *4*, 1.
(58) CRAVEN, J.: South. Med. & Surg., 1935, *97*, 192.
(59) CRICH, A.: Canad. M. A. J., 1932, *26*, 662.
(60) CRUTCHFIELD: In discussion of Haase, Hall and Marshall's paper (1922).
(61) DA FONSECA, O., AND LEAO, A. E. DE A.: Sciencia med., 1927, *5*, 615.
(62) D'AUNOY, R., AND BEVEN, J. L.: J. Lab. & Clin. Med., 1930–31, *16*, 124.
(63) DAVIS, B. F.: J. Infect. Dis., 1911, *8*, 190.
(64) DEMONBREUN, W. A.: Arch. Dermat. & Syph., 1935, *31*, 831.
(65) DENNIS, F. L.: Ann. Otol., Rhin. & Laryng., 1918, *27*, 571.
(66) DESJARDINS, A. U.: Am. J. Roentgenol., 1925, *14*, 14.
(67) DICKSON, E. C.: Arch. Int. Med., 1915, *16*, 1028.
(68) DODGE, C. W.: Medical mycology, 1935, C. V. Mosby Co.
(69) DOWLING, G. B., AND ELSWORTHY, R. R.: Proc. Roy. Soc. Med., 1925, *19*, dermatological section, 4.
(70) DOWNING, J. G.: New England J. Med., 1931, *204*, 1259.
(71) DYER, I.: J. Cutan. & G. U. Dis., 1901, *19*, 14.
(72) EISENDRATH, D. N.: Illinois M. J., 1905, *7*, 454.
(73) EISENDRATH, D. N., AND ORMSBY, O. S.: J. A. M. A., 1905, *45*, 1045.
(74) EISENSTAEDT, J. S., AND BOUGHTON, T. H.: Arch. Int. Med., 1914, *13*, 617.
(75) EVANS, N.: J. A. M. A., 1903, *40*, 1772.
(76) FAIRFIELD, W. E., AND KISPERT, R. W.: Wisconsin M. J., 1928, *27*, 69.
(77) FINNERUD, C. W.: M. Clin. North America, 1929, (Chicago no.) *13*, 452.
(78) FISCHKIN, E. A.: Illinois M. J., 1903, *5*, 472.
(79) FONTAINE, B. W., HAASE, M., AND MITCHELL, R. H.: Arch. Int. Med., 1909, *4*, 101.
(80) FORSBERG, C. W., AND STERN, M. A.: Journal Lancet, 1929, *49*, 498.
(81) FOWLER, R. H.: Long Island M. J., 1909, *3*, 423.
(82) FRICK, W.: J. Missouri M. A., 1917, *14*, 158.
(83) GARR, C. C.: Surg., Gynec. & Obst., 1925, *41*, 490.
(84) GASPAR, I.: Arch. Neurol. & Psychiat., 1929, *22*, 475.
(85) GASPAR, I., FENSTERMACHER, W. A., AND LINGEMAN, L. R.: Radiology, 1932, *18*, 305.
(86) GILCHRIST, T. C.: J. Cutan. & G. U. Dis., 1894, *12*, 496.
(87) GILCHRIST, T. C.: Johns Hopkins Hosp. Reports, 1896, *1*, 269.
(88) GILCHRIST, T. C.: Brit. M. J., 1902, vol. *2*, 1321.
(89) GILCHRIST, T. C., AND STOKES, W. R.: Bull. Johns Hopkins Hosp., 1896, *7*, 129.
(90) GILCHRIST, T. C., AND STOKES, W. R.: J. Exper. Med., 1898, *3*, 53.
(91) GILLIES, M.: Canad. M. A. J., 1933, *29*, 183.
(92) GOOD, R. W.: U. S. Vet. Adm. M. Bull., 1932, *8*, 490.
(93) GRAVES, M. L.: Am. J. Trop. Med., 1922, *2*, 123.
(94) GRAVES, S.: Kentucky M. J., 1923, *21*, 199.
(95) GREENFIELD, J. G.: Med. Science, 1924, *10*, 267.
(96) GRSCHEBIN, S.: Dermat. Wchnschr., 1927, *85*, 1049.

(97) Grschebin, S. N., and Maschkilleisson, L. N.: Ibid., 1926, *82*, 780; cont. Ibid., 1926, *82*, 811.
(98) Haase, M., Hall, E. R., and Marshall, C. H.: J. A. M. A., 1922, *79*, 820.
(99) Hamblen, E. C., Baker, R. D., and Martin, D. S.: Am. J. Obst. & Gynec., 1935, *30*, 345.
(100) Hamilton, C. M.: South. M. J., 1926, *19*, 431.
(101) Harding, D. B., and Garr, C. C.: Ibid., 1933, *26*, 315.
(102) Harris, F. G.: Am. J. M. Sc., 1901, *121*, 561.
(103) Hedge, H. M.: J. A. M. A., 1928, *90*, 1367.
(104) Hektoen, L.: Ibid., 1899, *33*, 1383.
(105) Herrick, J. B.: Ibid., 1907, *49*, 328.
(106) Hessler, R.: Indiana M. J., 1898, *17*, 48.
(107) Hildreth, E. R., and Sutton, A. C.: J. A. M. A., 1914, *63*, 2289.
(108) Hill, H. P., and Dickson, E. C.: California J. M., 1914, *12*, 120.
(109) Howes, W. B., and Morse, P. F.: Boston M. & S. J., 1921, *185*, 315.
(110) Hurley, T. D.: J. Med. Res., 1915, *33*, 499.
(111) Hyde, J. N.: J. A. M. A., 1905, *45*, 847.
(112) Hyde, J. N., Hektoen, L., and Bevan, A. D.: Brit. J. Dermat., 1899, *11*, 261.
(113) Hyde, J. N., and Ricketts, H. T.: J. Cutan. & G. U. Dis., 1901, *19*, 44.
(114) Iglauer, S.: Ann. Otol., Rhin. & Laryng., 1930, *39*, 56.
(115) Irons, E. E., and Graham, E. A.: J. Infect. Dis., 1906, *3*, 666.
(116) Jackson, E.: J. A. M. A., 1915, *65*, 23.
(117) Jackson, H.: Arch. Int. Med., 1914, *13*, 607.
(118) Jackson, R. H.: Am. J. Surg., 1926, *1*, 185.
(119) Jannin, L.: Les "Mycoderma," 1913, These de Nancy, 1001, p. 248.
(120) Jones, T. B.: Surg., Gynec. & Obst., 1930, *50*, 972.
(121) Keith, D. Y.: Urol. & Cutan. Rev., 1922, *26*, 27.
(122) Keith, D. Y.: Radiol. Rev. & Chicago M. Rec., 1933, *55*, 54.
(123) Kessler, J. B.: J. A. M. A., 1907, *49*, 550.
(124) King, J. M.: J. Tennessee M. A., 1920, *12*, 319.
(125) Kingsmith, D., Trow, E. G., and Dixon, H. A.: Arch. Dermat. & Syph., 1932, *25*, 178.
(126) Krost, R. A., Stober, A. M., and Moes, M. J.: Arch. Int. Med., 1914, *13*, 557.
(127) Langdon, J. F.: Nebraska M. J., 1922, *7*, 172.
(128) Le Count, E. R.: Johns Hopkins Hosp. Bull., 1915, *26*, 315.
(129) Le Count, E. R., and Myers, J.: J. Infect. Dis., 1907, *4*, 187.
(130) Lewis, D.: Surg. Clin. of Chicago, December, 1917, 1125.
(131) Lewis, B., Carroll, G., and Stryker, G. B.: J. A. M. A., 1930, *94*, 1987.
(132) Lewison, M., and Jackson, H.: Arch. Int. Med., 1914, *13*, 575.
(133) Lewtschanowski, N. M.: Klin. Ztschr. d. Univ. zu Saratov., 1928, *5*, 479.
(134) Litterer, W.: South. M. J. 1908, *1*, 294.
(135) Litterer, W.: Gulf States J. M. & S., 1909, *15*, 560.
(136) Livingston, S. K.: J. Bone & Joint Surg., 1935, new series *17*, 499.
(137) Long, E. R.: J. A. M. A., 1926, *87*, 1441.
(138) Longenecker, C. W.: J. Kansas M. Soc., 1912, *12*, 19.
(139) Lyle, H. M.: Kansas City Med. Index—Lancet, 1905, *26*, 329.
(140) MacBryde, C. M., and Thompson, E. I.: Arch. Dermat. & Syph., 1933, *27*, 49.
(141) MacGowan, G.: South. California Pract., 1906, *21*, 148.
(142) MacLane, C. C.: J. Infect. Dis., 1916, *19*, 194.
(143) Maner, G. D., and Hammack, R. W.: California & West. Med., 1930, *32*, 87.

(144) MARQUARDT, C. R.: J. Urol., 1936, *35*, 531.
(145) MARSHALL, C. H.: Memphis M. J., 1929, *6*, 218.
(146) MARTIN, D. S.: J. Infect. Dis., 1935, *57*, 291.
(147) MARTIN, D. S., AND SMITH, D. T.: J. Lab. & Clin. Med., 1935–36, *21*, 1289.
(148) MASCHKILLEISSON, L. N.: Dermat. Wchnschr., 1926, *83*, 1236; cont'd. Ibid., 1926, *83*, 1271.
(149) MCCOY, J. N.: Urol. & Cutan. Rev., 1922, *26*, 29.
(150) MCDONALD, O. H.: U. S. Vet. Bur. M. Bull., 1930, *6*, 502.
(151) MCKEE, S. H.: Internat. Clin., 1926, 36th series, vol. *3*, 50.
(152) MCKENNA, C. H.: Illinois M. J., 1933, *64*, 68.
(153) MCKENTY, F. E., AND MORGAN, D.: Ann. Surg., 1915, *61*, 513.
(154) MEDLAR, E. M.: Am. J. Path., 1927, *3*, 305.
(155) MELLON, R. R.: J. Bact., 1926, *11*, 229.
(156) MICHELSON, I. D.: J. A. M. A., 1928, *91*, 1871.
(157) MILLARD, R. I.: J. Arkansas M. Soc., 1932, *29*, 107.
(158) MILLARD, S. T., AND GODDARD, W. B.: J. Kansas M. Soc., 1926, *26*, 47.
(159) MILLER, W. S.: Tr. Nat. Tuberc. Assn., 1927, *23*, 230.
(160) MILLER, W. S.: Am. J. Path., 1927, *3*, 315.
(161) MONTGOMERY, F. H.: J. A. M. A., 1902, *38*, 1486.
(162) MONTGOMERY, F. H.: J. Cutan. Dis. incl. Syph., 1907, *25*, 393.
(163) MONTGOMERY, F. H., AND ORMSBY, O. S.: Arch. Int. Med., 1908, *2*, 1.
(164) MONTGOMERY, F. H., AND RICKETTS, H. T.: J. Cutan. & G. U. Dis., 1901, *19*, 26.
(165) MONTGOMERY, H.: M. Clin. North America, 1930, (Mayo Clinic No.) *14*, 651.
(166) MOORE, J. T.: Surg., Gynec. & Obst., 1920, *31*, 590.
(167) MOORE, M.: Ann. Missouri Bot. Garden, 1933, *20*, 79.
(168) MORRIS, R. T.: J. A. M. A., 1913, *61*, 2043.
(169) MULLIN, C. L.: West. Med. Rev., 1908, *13*, 482.
(170) MYERS, H. J., AND STOBER, A. M.: Arch. Int. Med., 1914, *13*, 585.
(171) NEW, G. B.: J. A. M. A., 1917, *68*, 186.
(172) NEW, G. B.: Ann. Otol., Rhin. & Laryng., 1928, *37*, 240.
(173) NEW, G. B.: Surg. Clin. North America, August, 1933, *13*, 869.
(174) NOMLAND, R.: Arch. Dermat. & Syph., 1935, *32*, 924.
(175) NUTE, A. J.: Boston M. & S. J., 1915, *173*, 881.
(176) OBEREMBT, B. H.: St. Paul M. J., 1908, *10*, 84.
(177) OPPENHEIMER, G. D.: J. Mt. Sinai Hosp., 1934, *1*, 128.
(178) ORMSBY, O. S.: Internat. Clin., 1917, 27th series, vol. *3*, 83.
(179) ORMSBY, O. S., AND MILLER, H. M.: J. Cutan. Dis. incl. Syph., 1903, *21*, 121.
(180) OTA, M., AND KAWATSURE, S.: Arch. f. Dermat. u. Syph., 1933–34, *169*, 149.
(181) OULMANN: J. Cutan. Dis. incl. Syph., 1911, *29*, 398.
(182) OULMANN: Ibid., 1911, *29*, 456.
(183) OULMANN: Arch. Dermat. & Syph., 1922, *6*, 381.
(184) OWENS, J. E., EISENDRATH, D. N., AND READY, C. F. W.: Ann. Surg., 1899, *30*, 545.
(185) PARKER, C. A.: J. Bone & Joint Surg., 1923, *5* (new series), 759.
(186) PARMENTER, F. J., AND SIMPSON, B. T.: J. Urol., 1919, *3*, 449.
(187) PAUTRIER, L. M., AND GLASSER, R.: Bull. Soc. franç. de dermat. et syph., 1934, *41*, 1452.
(188) PHALEN, J. M., AND NICHOLS, H. J.: Philippine J. Sc., 1908, *3*, Sec. B., 395.
(189) POLLACCI, G., AND NANNIZZI, A.: In BLANKENHORN AND GAMMEL (20).
(190) POTTER, H. E.: Am. Quart. Roentgenol., 1910, *2*, 243.
(191) PUESTOW, K. L.: Wisconsin M. J., 1926, *25*, 141.

(192) PUSEY, W. A.: J. Cutan. Dis. incl. Syph., 1903, *21*, 223.
(193) RAIFORD, T. S.: Johns Hopkins Hosp. Bull., 1932, *51*, 61.
(194) RAVOGLI, A.: Lancet Clinic, 1911, *105*, 489.
(195) RAVOGLI, A.: Arch. f. Dermat. u. Syph., 1912, *112*, 847.
(196) RAVOGLI, A.: Acta dermat.-venerol., 1925, *6*, 281.
(197) REDAELLI, P., AND CIFERRI, R.: J. Trop. Med., 1934, *37*, 280.
(198) REED, P. A.: Nebraska M. J., 1926, *11*, 257.
(199) REWBRIDGE, A. G., DODGE, C. W., AND AYERS, T. T.: Am. J. Path., 1929, *5*, 349.
(200) RICKETTS, H. T.: J. Med. Res., 1901, *6*, 373.
(201) RICKETTS, H. T.: J. Boston Soc. M. Sc., 1901, *5*, 453.
(202) RILEY, F. B., AND LE COUNT, E. R.: Arch. Int. Med., 1914, *13*, 614.
(203) ROBINSON, H. M.: Bull. School Med. Univ. Maryland, 1931, *16*, 89.
(204) ROBINSON, H. M.: Arch. Dermat. & Syph., 1933, *28*, 219.
(205) ROSENTHAL, J. M.: J. Lab. & Clin. Med., 1934–35, *20*, 1164.
(206) ROTTER, W., AND CHAVARRIA, P.: Arch. f. Schiffs-u. Tropen-Hyg., 1933, *37*, 1.
(207) RUSK, G. Y., AND FARNELL, F. J.: Univ. California Publ., Path., 1912, *2*, 47.
(208) RUTLEDGE, W. U.: Kentucky M. J., 1933, *31*, 335.
(209) RYERSON, E. W.: Am. J. Orth. Surg., 1908, *6*, 79.
(210) RYPINS, E. L.: Radiology, 1934, *22*, 77.
(211) SANDERSON, E. S., AND SMITH, D. C.: Arch. Dermat. & Syph., 1927, *16*, 153.
(212) SCHWARTZ, V. J.: Arch. Ophth., 1931, *5* (new series), 581.
(213) SHAFFNER, P. F.: Arch. Int. Med., 1914, *13*, 621.
(214) SHAW, F. W., AND MEADOR, B. W.: Virginia M. Monthly, 1932–33, *50*, 419.
(215) SHEPHERD, F. J., AND RHEA, L. I.: J. Cutan. Dis. incl. Syph., 1911, *29*, 588.
(216) SHIELDS, E. H.: Ibid., 1909, *27*, 156.
(217) SIHLER, W. F., PEPPARD, T. A., AND COX, J. W.: Journal Lancet, 1917, *37*, 253.
(218) SIMPSON, F. E.: J. A. M. A., 1914, *62*, 844.
(219) SMITH, A. J.: Univ. Pennsylvania M. Bull., 1909–10, *22*, 362.
(220) SMITH, C. H.: U. S. Vet. Adm. M. Bull., 1935–36, *12*, 197.
(221) SMITH, D. C., TURNER, H. C., AND SANDERSON, E. S.: Brit. J. Dermat., 1928, *40*, 344.
(222) SNOKE, J. H., AND STRICK, E. J.: J. A. M. A., 1912, *59*, 2056.
(223) STEIN, R. O.: Arch. f. Dermat. u. Syph., 1914, *120*, 889.
(224) STELWAGON, H. W.: Am. J. M. Sc., 1901, *121*, 176.
(225) STOBER, A. M.: Arch. Int. Med., 1914, *13*, 509.
(226) SUGDEN, F.: Brit. M. J., 1923, vol. *2*, 63.
(227) SUTTON, R. L.: J. A. M. A., 1913, *60*, 115.
(228) SWIFT, H., AND BULL, L. B.: M. J. Australia, 1917, *2*, 265.
(229) THOMPSON, C.: Louisville Monthly J. M. & S., 1913–14, *20*, 311.
(230) TOEPEL, T.: J. A. M. A., 1929, *93*, 32.
(231) TYAU, E. S.: China M. J.; 1918, *32*, 234.
(232) VARNEY, H. R.: Am. J. Dermat. & G. U. Dis., 1908, *12*, 188.
(233) VINSON, P. P., BRODERS, A. C., AND MONTGOMERY, H.: Surg., Gynec. & Obst., 1928, *46*, 255.
(234) VUILLEMIN in GEDOELST: 1902, Les champignons parasites de l'homme et des animaux domestiques, H. Lamertin, Brussels, p. 45.
(235) WADE, H. W., AND BEL, G. S.: Arch. Int. Med., 1916, *18*, 103.
(236) WALKER, J. W., AND MONTGOMERY, F. H.: J. A. M. A., 1902, *38*, 867.
(237) WANAMAKER, A. T.: Tr. Am. Laryng., Rhin. & Otol. Soc., 1928, *34*, 450.
(238) WASHBURN, R. G.: J. A. M. A., 1911, *56*, 1095.
(239) WELLS, H. G.: New York M. J., 1898, *67*, 427.

(240) WENDE: 1919. Quoted by PARMENTER AND SIMPSON (186).
(241) WERLEY, G.: Southwestern Med., 1920, *4*, 4.
(242) WILDER, W. H.: J. A. M. A., 1904, *43*, 2026.
(243) WILHELMJ, C. M.: Am. J. M. Sc., 1925, *169*, 712.
(244) WILLMOT, C. B.: 1933. In discussion of paper by RUTLEDGE (208).
(245) WING, H. J.: Illinois M. J., 1935, *67*, 551.
(246) WOHL, M. G.: West. Med. Rev., 1916, *21*, 171.
(247) WOHL, M. G.: J. A. M. A., 1923, *81*, 647.
(248) WOOD, C. A.: Ann. Ophth., 1904, *13*, 92.
(249) YOUNG, W. J.: Kentucky M. J., 1922, *20*, 156.

CLIMATIC AND SOCIO-ECONOMIC FACTORS IN MORTALITY FROM PULMONARY TUBERCULOSIS[1, 2]

I. M. MORIYAMA AND L. P. HERRINGTON

Since the time of Hippocrates a large volume of material has found its way into the literature emphasizing the importance of medical climatology, with particular reference to the therapeutic effects of certain meteorological environments on tuberculosis. Since many of the claims made in regard to climatic influences are biased accounts of the merits of various health resorts, too much importance cannot be attached to these statements. However, as in the case of most respiratory diseases, it appears evident that climate may play a rôle in the aetiology of tuberculosis.

A review of the literature reveals various conceptions as to what constitutes a favorable or unfavorable climatic situation for this disease. The meteorological factors which have been most frequently associated are: (*1*) altitude, as affecting certain pressure and climatic relationships; (*2*) precipitation; (*3*) humidity; (*4*) sunshine; (*5*) temperature; and (*6*) temperature variability.

The high altitude theory of tuberculosis immunity was proposed in Europe in 1840 by Smith (cited by Gordon, 1913), who announced that high altitudes were in some way antagonistic to the disease. The subject is adequately reviewed by Gordon (1913). It appears from this review that the concept of altitude in relation to tuberculosis was enthusiastically received and universally accepted. Gordon, however, concludes from his study of climatology and tuberculosis that

> (*1*) altitude of itself has no evident effect on the mortality from phthisis, such as has been supposed to exist—in other words, that increasing altitude does not, of itself, appreciably decrease phthisis prevalence; (*2*) altitude has, however, through exposure to rain-bearing winds just the reverse effect, the prevalence increasing with the altitude, this being presumably due to increasing exposure to these winds; (*3*) there is some support for Lombard's view that

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[2] Based on a portion of a dissertation submitted by the senior author in fulfilment of requirements for the degree of Doctor of Philosophy in Yale University, 1937.

an intermediate zone of increased phthisis prevalence exists, roughly corresponding to the zone of maximum humidity and rainfall, at least in exposure to rain-bearing winds.

Later studies by Ichok (1922) in France, Rogers (1925) in India, and Gordon and Asher (1928) in England, also emphasized the importance of precipitation and humidity in relation to tuberculosis. Ichok (1922), however, believed that altitude was also a significant factor. Gardiner, Webb and Ryder (1923) investigated the relationship between tuberculosis mortality in the United States and altitude, humidity and density of population, and found that, in general, the states which showed the highest mortality were those which combined low altitude, high humidity and marked density of population.

In regard to temperature as related to tuberculosis mortality, Cline (1895) found that deaths occurred more frequently on days with abnormally high or abnormally low temperature than on days when the temperature was normal. (The temperature was considered abnormal when it was 8° above or below the normal temperature.) Gray (1926), in studying the effect of intraseasonal variations in weather, also found that extremes in temperature were associated with high tuberculosis mortality rates but the evidence was not considered to be conclusive.

The influence of daily variations in temperature and tuberculosis mortality was noticed by Cline (1895) who reported that days with plus changes in temperature were characterized by a large increase in the number of deaths from tuberculosis as compared to the frequency of deaths occurring on days with a "stationary" temperature. Conversely, days on which minus changes, or drops, in temperature occurred were found to be accompanied by a significant decrease in the number of tuberculosis deaths. These findings were verified to some degree by the clinical experience of Piéry and Faury (1922) who observed that sudden falls in temperature were not found to produce any serious effect but that excessive heat following a cold period was often associated with insomnia, anorexia and slight pulmonary congestion.

Mills (1935) studied the mortality statistics of the Hamilton County Tuberculosis Sanatorium to demonstrate a relationship between seasonal variations in the onset of tuberculosis and the degree of storminess as measured by temperature variability. In the same study, Mills attempted to find some relationship between climate and tuberculosis mortality by his method of contour or iso-death lines. His general conclusion from this study was that tuberculosis mortality in the United

States was associated with the course of polar waves. The validity of this conclusion is open to question since an examination of Mills's iso-death lines in his city curves clearly shows that the contours were not properly interpolated; while his state graph reveals little but the high mortality belt in Kentucky and Tennessee. This high mortality belt has been extensively studied of late (Dauer and Lumsden, 1937), but it bears no significant relation to climate.

The study of tuberculosis in relation to climate is complicated, not only by the meteorological factors themselves, but by other considerations such as race, age, sex, occupation, density of population, economic status, etc., not to mention the importance of preventive measures instituted against the disease. In the present paper we intend to analyze the independent association between pulmonary tuberculosis mortality, on the one hand, and climatic and socio-economic factors on the other.

Our mortality data represent the average pulmonary tuberculosis death rate for the ten-year period 1921–1930, inclusive, in each of 44 states[3] in the United States Registration Area. These rates refer to a specific age range (10 to 25 years). This age group was selected as being that least liable to be affected by occupational hazards leading to tuberculosis.

Table 1 shows the tuberculosis mortality statistics. The eleven climatic and eleven socio-economic factors to be studied are listed below, but values corresponding to each of these factors will not be presented here, since they have already been reproduced in a previous paper (Herrington and Moriyama, 1938), in which the statistical procedures employed are fully discussed.

Number	*Climatic Variables*
1	Normal temperature in °F.
2	Relative humidity in per cent
3	Average wind movement in miles per hour
4	Intensity of solar radiation
5	Normal precipitation rate in inches
6	Annual frequency of cyclones
7	Annual frequency of anticyclones
8	Day to day temperature variability in °F.
9	Daily temperature range in °F.
10	Monthly temperature range in °F.
11	Annual temperature range in °F.

[3] Data for New Mexico and Mississippi were excluded due to doubtful reliability of mortality statistics. Reliability was based upon percentage of deaths (arbitrary permissible limit 10 per cent) reported as deaths due to ill defined causes. South Dakota and Texas had no data prior to 1930.

Number	*Socio-Economic Variables*
12	Per cent of urban population
13	Population density per square mile
14	Annual per capita effective income in dollars
15	Number of residence telephones per 100 population
16	Per capita value of products in dollars
17	Per cent of English in total population
18	Per cent of Irish in total population
19	Per cent of Scandinavian in total population
20	Per cent of German in total population
21	Per cent of Italian in total population
22	Per cent of Negro in total population

TABLE 1

Tuberculosis mortality rates by states (rates per 100,000 population between 10–25 years of age)

STATES	MORTALITY RATES	STATES	MORTALITY RATES
Alabama	68.8	Montana	35.6
Arizona	23.9	Nebraska	18.4
Arkansas	56.4	Nevada	58.2
California	93.5	New Hampshire	40.7
Colorado	94.2	New Jersey	57.4
Connecticut	55.2	New York	60.9
Delaware	79.1	North Carolina	74.2
Florida	61.7	North Dakota	33.3
Georgia	65.5	Ohio	57.8
Idaho	29.2	Oklahoma	38.3
Illinois	55.2	Oregon	42.9
Indiana	56.4	Pennsylvania	53.5
Iowa	21.5	Rhode Island	58.9
Kansas	30.9	South Carolina	84.2
Kentucky	80.3	Tennessee	98.0
Louisiana	77.3	Utah	11.5
Maine	51.1	Vermont	40.6
Maryland	92.7	Virginia	88.2
Massachusetts	57.6	Washington	57.3
Michigan	58.0	West Virginia	52.3
Minnesota	43.7	Wisconsin	46.0
Missouri	58.2	Wyoming	24.9

In table 2 we have summarized the product-moment correlation coefficients between tuberculosis mortality and our 22 variables. Inspection of the primary correlations yields four variables (normal temperature, precipitation rate, frequency of cyclones and annual temperature range) in the climatic group, and three variables (per capita value of products, per cent of Scandinavians and per cent of Negroes) in the socio-economic group which are conspicuously high in their association

with tuberculosis. The climatic correlations indicate that tuberculosis mortality tends to be high in warm, rainy climates characterized by small temperature variability. The socio-economic correlations suggest that tuberculosis mortality occurs more frequently in areas with a large Negro population where the economic status, as measured by value of products, is low.

The zero order correlations observed between pulmonary tuberculosis and climatic factors were not significantly altered when the factor of income, population density or urbanization was held constant. The

TABLE 2

Zero order correlation coefficients between tuberculosis mortality and climatic and socio-economic factors*

Normal temperature	+.44	Per cent urban population	+.11
Relative humidity	+.26	Population density	+.33*
Wind velocity	−.01	Per capita income	−.06
Solar radiation	+.05	Residence telephones	−.36*
Precipitation	+.55	Per capita value of products	−.62
Frequency of cyclones	−.39	Per cent English	−.37*
Frequency of anticyclones	−.30*	Per cent Irish	−.04
Day–day temperature variations	−.08	Per cent Scandinavian	−.42
Daily temperature range	−.36*	Per cent German	−.28
Monthly temperature range	−.31*	Per cent Italians	+.11
Annual temperature range	−.48	Per cent Negro	+.51

* The assessment of reliability of the correlation coefficients is based upon the "t" test as given by Fisher (1930). In the presentation of results, the highly significant correlation coefficients ($P > .01$) are underlined and the doubtfully significant values ($P = .05$ to .01), that is, the coefficients falling in between the lowest significant values and the lowest highly significant limits, are denoted by an asterisk.

climatic correlations, however, were markedly influenced by the introduction of a racial factor, proportion of Negroes, and an economic index, per capita value of products. The effect of these factors on the partial correlation coefficients may be seen from the following summary:

		Factor Held Constant	
Tuberculosis vs.	*Zero Order*	*Per cent Negro*	*Per Capita Value of Products*
Normal temperature	+0.48	+0.14	+0.03
Cyclones	−0.39	−0.22	−0.15
Anticyclones	−0.29	+0.05	−0.01
Precipitation	+0.55	+0.34*	+0.27
Daily temperature range	−0.36*	−0.26	−0.19
Day–day temperature variations	−0.08	+0.02	+0.17
Monthly temperature range	−0.31*	−0.14	−0.03
Annual temperature range	−0.48	−0.31*	−0.20

The effect of value of products in the partial correlation analysis is particularly striking. When this measure of natural wealth was held constant all of the climatic correlations were reduced to statistical nonsignificance. The influence of the racial factor, Negroes, on the climatic correlations was less marked but it was statistically successful in affecting all of the significant correlations between pulmonary tuberculosis mortality and the meteorological factors. All but two climatic correlations were lowered to nonsignificant associations and these, precipitation and annual temperature range, became of doubtful statistical significance when the Negro factor was held constant. These results indicate that certain of the socio-economic factors are important considerations in pulmonary tuberculosis mortality.

The relationship between tuberculosis mortality and per capita value of products and percentage of Negroes is further emphasized by the graphical analysis as presented in figure 1. It may be seen that there is an inverse relationship between tuberculosis mortality and value of products. There is also a definite line of demarcation in mortality rates, the states with high proportion of Negroes (over 10 per cent of the total population) exhibiting, in every case, high tuberculosis mortality. It is to be noted that the two states which fall away from this trend are Colorado and California. The high tuberculosis mortality for these two states may be attributed to the concentration of sanatoria in those states.

In reference to the rural-urban distribution of pulmonary tuberculosis mortality, it may be said that a superficial examination of the data shows nothing to indicate a relationship between tuberculosis and rurality or urbanization. However, further study shows that certain states with unduly high mortality rates are vitiating the results. The tuberculosis mortality rates for Colorado, California,[4] and states with a Negro population in excess of 10 per cent of the total population were found to be obscuring a relationship which was revealed when data for the states mentioned above were excluded. When these states with divergent rates were eliminated, the relationship between tuberculosis and urbanization became evident. As shown in figure 2, the mortality curve is seen to rise with the increase in the degree of urbanization up to a certain point, and then flattens out. The inflection in the curve occurs near

[4] Since a good proportion of the tuberculosis mortality of Colorado and California is composed of nonresident deaths occurring in sanatoria, it was felt that data for these two states could be disregarded with justification.

the point at which the population characteristic of the state is 50 per cent urban and 50 per cent rural. It appears from this curve that the tuberculosis mortality rates are generally low in states which are pre-

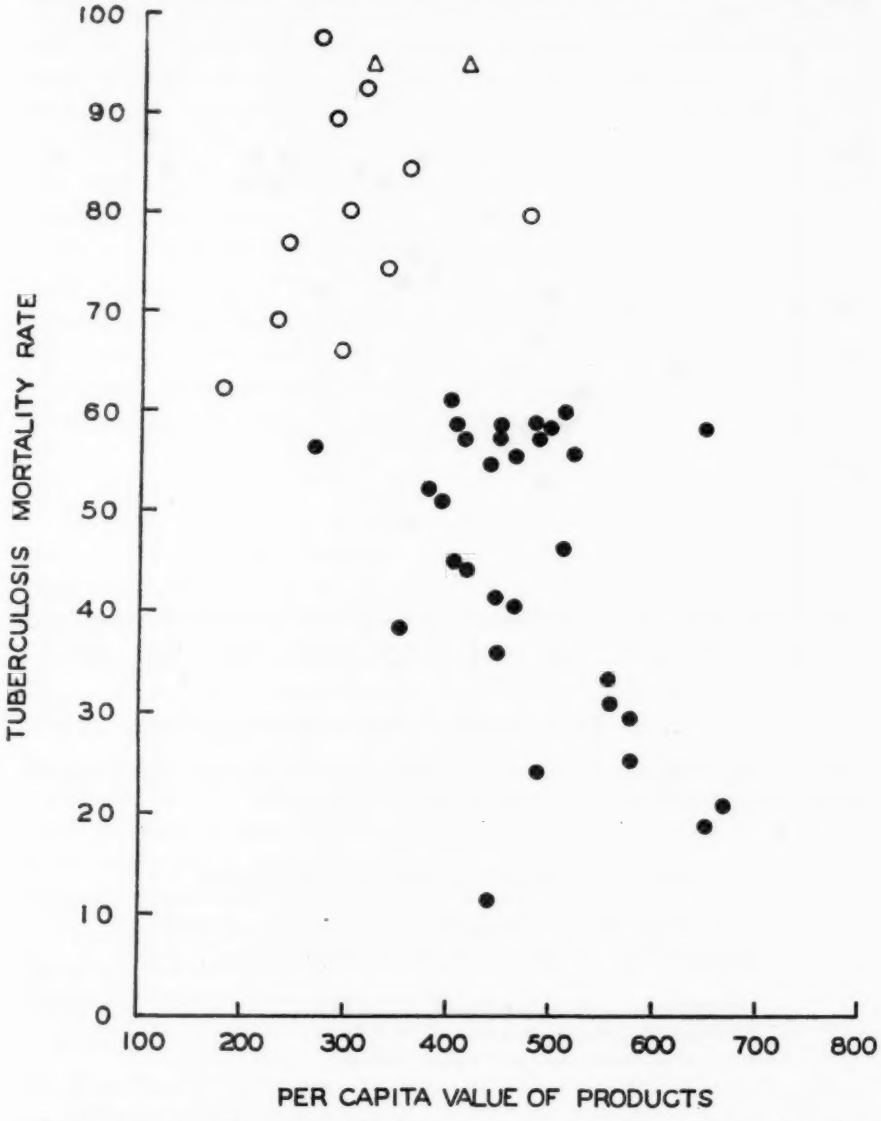

FIG. 1. Relationship between tuberculosis mortality rate and per capita value of products. ○ = states with high proportion (over 10 per cent) of Negro population; △ = Colorado and California; ● = other states.

dominantly rural in character, but as the states become more urbanized the mortality rate tends to increase up to a "saturation" point.

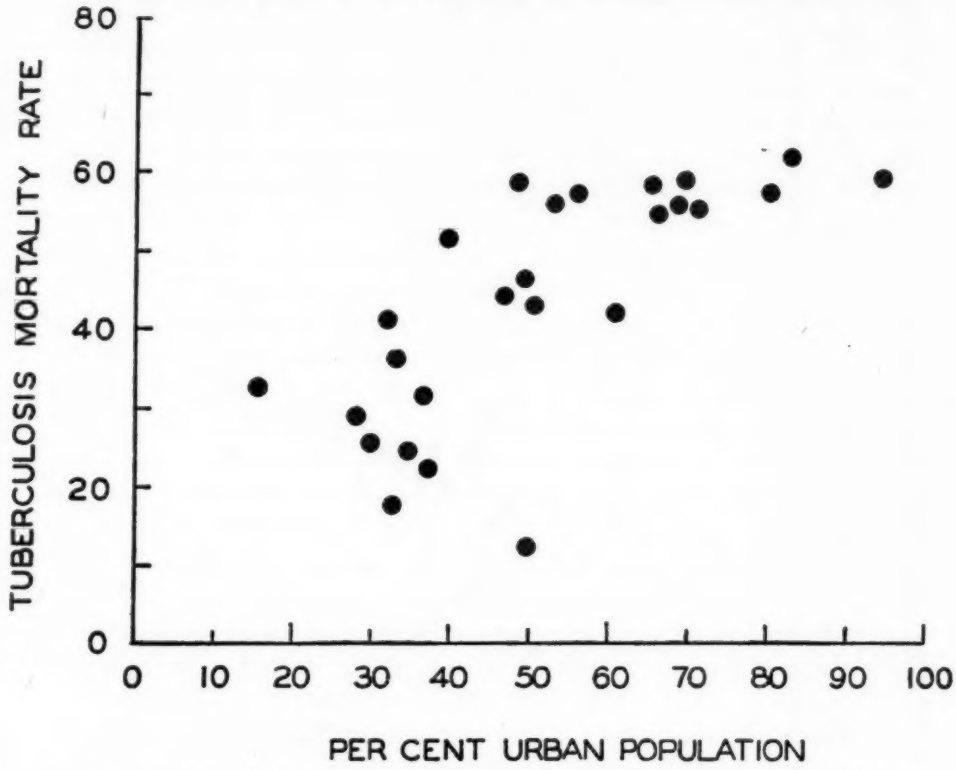

FIG. 2. Relationship between tuberculosis mortality rate and per cent urban population in states with less than 10 per cent Negroes in the total population.

TABLE 3

Coefficients of multiple and combined partial correlation

$R_{(Tbc).(Climatic\ Factors)} = R_{(Tbc).(Precip)(Annual\ Temp.\ Range)}$	$= 0.66$
$R_{(Tbc).(Socio\text{-}Econ.\ Factors)} = R_{(Tbc).(Pop.\ Density)(Val.\ of\ Prod.)}$	$= 0.70$
$r_{(Tbc)(Clim.\ Factors).(Socio\text{-}Econ.\ Factors)}$	$= 0.29$
$r_{(Tbc)(Socio\text{-}Econ.\ Factors).(Clim.\ Factors)}$	$= 0.41$
$R_{(Tbc).(Clim.\ Factors)(Socio\text{-}Econ.\ Factors)}$	$= 0.73$

In a previous paper (Herrington and Moriyama, 1938) we have described a method which makes it possible to consider two groups of independent variables (climatic and socio-economic) separately and to

compare the relative degree of purely statistical association between the factors in each group considered jointly and disease mortality. When this technique was applied to this problem, two factors (precipitation and annual temperature range) were isolated from the climatic group and two variables (population density and value of products) were isolated from the socio-economic panel as being factors most closely associated with tuberculosis mortality. The relative importance of the climatic and socio-economic group as entities was then estimated through the method of combined partials (Stouffer, 1934). These results are summarized in table 3.

Thus, it appears that both climatic and socio-economic factors may have some statistical significance. The partial correlation of .29 with climatic factors (high precipitation and small difference between summer and winter temperature) is statistically nonsignificant. The correlation of .41 with socio-economic factors (more urban and less prosperous communities, as measured by value of products) is distinctly significant.

DISCUSSION

The most recent study of climate as related to tuberculosis is probably that of Cowles and Chapman (1935). These investigators did not limit themselves merely to the consideration of climatic factors but also included certain socio-economic factors which they believed to be of importance. Their statistical analysis was based on the pulmonary tuberculosis mortality data for the white population, standardized with respect to age distribution. The conclusions from their study indicated that the climatic elements of possible importance were sunshine, precipitation, daily temperature range and altitude. The significance of these climatic factors, however, were found to be overshadowed by the more important socio-economic factors, namely, Negroes, illiteracy and expenditures made for educational purposes.

The results of the present study generally agree, insofar as the primary correlations are concerned, with those of Cowles and Chapman (1935). The results may be compared as follows:[5]

Tuberculosis Death Rate vs.	*Cowles and Chapman*	*This Study*
Annual average temperature	+0.306*	*+0.443*
Daily temperature range	*−0.511*	*−0.453*

[5] The data presented are only for climatic and socio-economic factors common to the two analyses, and do not include the complete series of zero order correlations.

Tuberculosis Death Rate vs.	*Cowles and Chapman*	*This Study*
Annual temperature range	−0.230	*−0.480*
Relative humidity	*+0.591*	+0.261
Sunshine	*−0.477*	+0.053
Wind	−0.214	−0.012
Precipitation	*+0.638*	*+0.550*
Per cent Negroes	*+0.510*	*+0.513*
Population density	+0.286	+0.333*
Per cent urban	+0.085	+0.109
Per capita income	−0.013	−0.059

From the data presented above it appears that the point of greatest discrepancy is in the relationship between tuberculosis mortality and sunshine. Cowles and Chapman obtained a highly significant negative correlation with this sunshine factor but no evidence of a significant association is indicated by the extremely low correlation coefficient found in the present study. Since the index of sunshine (average number of hours of sunshine per day computed from the average for each of the twelve months) used by Cowles and Chapman differs somewhat from the measure of intensity of solar radiation adopted in this study, it was thought that this might be the cause for the discrepancy. Tuberculosis mortality, from our data, was therefore correlated with the average daily duration of sunshine but the resulting coefficient of correlation (-0.16 ± 0.10) was not significant.

The results of this study, as well as those of Cowles and Chapman, clearly indicate why many of the previous investigators were successful in demonstrating certain climatic relationships with tuberculosis when only the meteorological aspects of the problem were considered. If we were to disregard the implication of the socio-economic correlations in the present investigation, we could readily arrive at the conclusion that certain climatic factors, namely, normal temperature, precipitation, solar radiation and temperature variability, are highly associated with tuberculosis mortality. However, as demonstrated by the partial correlation analysis, these climatic associations are chiefly an expression of superficial relationships resulting from accidental or incidental intercorrelations with other factors significantly related to tuberculosis. The statistical evidence presented indicates that climatic factors are not of independent significance in relation to tuberculosis, and that the correlations exhibited by the meteorological variables are in a large measure due to the influence of certain socio-economic factors.

The most significant sociological and economic factors which affect tuberculosis mortality have been found to be per cent of Negroes, per cent of urban population, population density and per capita value of products. These results are in general accord with those of other investigators. The effect of the racial factor, Negroes, on tuberculosis mortality has been demonstrated conclusively by Lee (1929), Whitney (1931, 1935), Parkhurst (1933), Wu and Winslow (1933), Cowles and Chapman (1935), Opie, McPhedran and Putnam (1936) and others. The other socio-economic factors named above have also been generally recognized as being of importance in relation to tuberculosis mortality. The rural to urban distribution of tuberculosis has been studied by DePorte (1928), Gray (1928), Whitney (1935), Korns (1931), Sydenstricker and Downes (1933), Parkhurst (1933) and others, all of whom are agreed that the prevalence of tuberculosis is higher in the urban districts. This relationship was confirmed in this study and results indicate that tuberculosis mortality is a curvilinear function of urbanization.

In regard to economic status in relation to tuberculosis, the results of this study indicate that tuberculosis mortality is inversely correlated with per capita value of products. Wu and Winslow's (1933) study also showed a negative correlation ($-0.326 \pm .014$). The absence of a correlation between income and tuberculosis was surprising, since it is generally believed that tuberculosis is associated with poverty. This finding, however, is not inconsistent with the results found by Wu and Winslow (1933) and Cowles and Chapman (1935). It should be mentioned in passing that Wu and Winslow's survey of mortality, prosperity and urbanization in 3,000 counties in the United States revealed a positive but low correlation ($r = 0.062 \pm .015$) between tuberculosis mortality and income. They attributed this association not to prosperity *per se* but to urbanization with its essential factor of industrialism.

In concluding this discussion, it may be said that climate is a relatively unimportant factor in tuberculosis. It might possibly be argued that high temperatures, as may be suggested by the significant climatic associations in the zero order analysis, may have a debilitating effect on resistance to the tubercle bacillus. Baetjer and Lange (1928), however, were unable to demonstrate any alteration in the susceptibility and resistance of guinea pigs to infection with a virulent strain of tubercle bacillus under experimental conditions of high temperature and humidity. At the present time there is little evidence weighing against the extension of this finding to human beings.

A word may be said in reference to the status of climate in tuberculosis therapy. There are various conceptions as to what constitutes an ideal climate for the treatment of tuberculosis but Trask (1917), Miller (1928), Knopf (1931), Bruns (1932) and others agree that certain climates are beneficial only to the extent that they permit patients to spend a maximum number of hours comfortably out of doors. A regimen of regulated rest and exercise, proper food and open air life is considered to be the fundamental essential in the treatment of tuberculosis, and the part played by climate is believed to be subservient to the other more important considerations.

BIBLIOGRAPHY

(1) Baetjer, A. M., and Lange, S. B.: The effect of high humidity and moderately high temperature on the susceptibility and resistance to tuberculosis in guinea pigs, Am. J. Hyg., 1928, *8*, 935.

(2) Bruns, E. H.: Climatic treatment in tuberculosis, Am. Rev. Tuberc., 1932, *26*, 124.

(3) Cline, I. M.: The climatic causation of disease; with chart showing pathological distribution of climate in the United States, Tr. Texas State M. A., 1895, *92*, 114.

(4) Cowles, A., and Chapman, E. N.: A statistical study of climate in relation to pulmonary tuberculosis, J. Am. Statis. A., 1935, *30*, 517.

(5) Dauer, C. C., and Lumsden, L. L.: Tuberculosis mortality in southeastern United States, Am. Rev. Tuberc., 1937, *35*, 43.

(6) DePorte, J. V.: Recorded and resident death rates from tuberculosis in New York State in 1926, Ibid., 1928, *17*, 634.

(7) Gardiner, C. F., Webb, G. B., and Ryder, C. T.: Tuberculosis mortality in relation to altitude, humidity and population density, Ibid., 1933, *8*, 112.

(8) Gordon, W.: The place of climatology in medicine, The Hyde Lectures, H. K. Lewis, London, 1913, p. 62.

(9) Gordon, W., and Asher, W. M.: The influence of strong rain bearing winds on the prevalence of phthisis, Brit. M. J., 1928, pt. 1, 337.

(10) Gray, G.: A study of the effect of intra-seasonal variations in weather on mortality from various causes, Ph.D. Dissertation, Yale University, 1928.

(11) Gray, C. E.: Tuberculosis mortality in the Original Death Registration States, Am. Rev. Tuberc., 1928, *18*, 687.

(12) Herrington, L. P., and Moriyama, I. M.: The relation of mortality from certain metabolic diseases to climatic and socio-economic factors, Am. J. Hyg., 1938, *28*, 396.

(13) Ichok, G.: La mortalité par la tuberculose dans les différentes régions climatiques de la France, Rev. de la tuberc., 1922, *3*, 267.

(14) Knopf, S. A.: Climate in tuberculosis and prevention of relapse, J. A. M. A., 1931, *96*, 2023.

(15) Korns, J. H.: Tuberculosis infection among school children in a rural area in New York State, Am. Rev. Tuberc., 1931, *24*, 532.

(16) Lee, W. W.: The epidemiology of tuberculosis, past and present, Ibid., 1929, *20*, 368.

(17) Miller, J. A.: Climate in the treatment of tuberculosis, Ibid., 1928, *18*, 523.

(18) Mills, C. A.: Susceptibility to tuberculosis, Am. J. M. Sc., 1935, *189*, 330.

(19) Opie, E. L., McPhedran, F., and Putnam, P.: Studies in tuberculosis, IV, V & VI, Am. J. Hyg., 1936, *23*, 493.

(20) PARKHURST, E.: Resident mortality from tuberculosis in urban and rural New York according to age, sex, color, and general nativity, Am. J. Pub. Health, 1933, *23*, 901.

(21) PIÉRY AND FAURY, G.: Variations atmosphériques et tuberculose pulmonaire, Progrès méd., June 10, 1922, p. 409; Abstract, Am. Rev. Tuberc., 1922–1923, *6*, 270.

(22) ROGERS, L.: Tuberculosis incidence in India, Brit. M. J., 1925, pt. 1, 225.

(23) STOUFFER, S. A.: A coefficient of "combined partial correlation" with an example from sociological data, J. Am. Statis. A., 1934. *29*, 70.

(24) SYDENSTRICKER, E., AND DOWNES, J.: The prevalence of tuberculosis infection in a rural community in New York State, Quart. Bull. Milbank Memorial Fund, 1933, *11*, 1.

(25) TRASK, J. W.: Climate and tuberculosis, U. S. Public Health Report, 1917, *32*, 318.

(26) WHITNEY, J. S.: Facts and figures about tuberculosis, Nat. Tuberc. Assn., New York, 1931, p. 63.

New and supplementary facts and figures about tuberculosis, Nat. Tuberc. Assn., New York, 1935, p. 46.

(27) WU, C. K., AND WINSLOW, C.-E. A.: Mortality, prosperity and urbanization in the U. S. counties, Am. J. Hyg., 1933, *18*, 491.

TREATMENT OF TUBERCULOSIS BY TUBERCULIN DESENSITIZATION[1, 2]

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The therapeutic use of tuberculin dates back to 1891 when Koch (1) announced the product as a cure for tuberculosis. Its use has been regarded as rational drug therapy since that time, but its overuse, underuse and misuse have led to its practical abandonment except in a certain few well defined circumstances. Koch sought to produce constitutional reaction with every dose of tuberculin. According to Hamman and Wolman (2), Koch thought "reactions cause beneficient inflammatory changes and, to obtain these reactions, the tuberculin is used. The effect of each dose had to be made evident and palpable to this pioneer of tuberculin therapy. If no clinical spectacle followed upon a dose of tuberculin, he inferred that he had been too cautious, and at once took a great stride so as to compensate for his previous slowness. He reported cures. Others reported deaths, numerous deaths." Thus entered the period of so called "tuberculin delirium" which crystallized the position taken during the first decade of this century that tuberculin had a useful place in the physician's armamentarium but with much more sharply limited indications than had been the case formerly, and that wisdom and skill and a knowledge of the pathology of tuberculosis were essential to the proper and successful use of the product.

Earlier work was predicated upon the contention that healing occurs as a result of the formation of fibrous tissue at the seat of the lesion—this having been stimulated by the irritation which the tuberculin caused. This contention was supported by considerable indirect evidence. For instance, in ocular tuberculosis, specific, focal inflammation appears within a few hours of the injection of tuberculin, reaches a height at about twenty-four hours and subsides by the third or fourth day. During the course of such treatment, scarring and fibrosis of the lesion become manifest and conspicuous; this reaction is presumably the fibrous

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sequence of the oft repeated inflammation. In patients with tuberculous adenitis, shrinking and scarring of the lesion almost regularly follows the usual course of tuberculin injection. In tuberculous animals the administration of tuberculin causes focal inflammation and repeated doses are followed by preternatural scarring of lesions.

During the last decade a great deal of work upon the question of desensitization by the use of tuberculin has reopened the issue of tuberculin treatment and may have revitalized it. Experiments in the hands of several workers have indicated that repeated and eventually very large doses of tuberculin obliterate allergy and the disadvantageous aspects of the constitutional and focal tuberculin reactions without, in any way, affecting the immunity which appears to inhere in the infected state. Other observers have granted the desensitization effects of such procedure but have indicated that certain deleterious and dangerous results lie in the wake of continued desensitization.

When the work here reported was begun in 1933, the indications were that desensitization in animals was without baneful effect. To make clinical application of this observation, fifteen patients of low skin sensitivity were given tuberculin daily in rather rapidly increasing doses over a period of several months, with due attention always to symptoms produced by the previous dose. The smallest dose given was 0.1 cc. of 1:1,000,000 dilution and the largest was 1 cc. of undiluted tuberculin. As a rule the initial dose was 0.1 cc. of 1:10,000 dilution. Doses were increased by 0.1 cc. per day by the scheme in general vogue. These and other germane data appear in table 1. Old Tuberculin and TPT were used interchangeably and each was used in each patient.[3]

The work was done in this manner purely as an experiment, and patients were chosen who had done poorly. The 15 patients had intract-

[3] The basic TPT solution from which dilutions were made contained 1.0 mg. per cc. Data are expressed in terms of dilution rather than by measured quantity because, obviously, there is no accurate measure of the active principle in Old Tuberculin. Figures used in the text have the following OT and TPT equivalents by dilution and by weight:

	OT		TPT
1 cc.	Undiluted	=	1.0 mg.
1 cc.	1:10 dilution	=	0.1 mg.
1 cc.	1:100 dilution	=	0.01 mg.
1 cc.	1:1000 dilution	=	0.001 mg.
1 cc.	1:10,000 dilution	=	0.000,1 mg.
1 cc.	1:100,000 dilution	=	0.000,01 mg.
1 cc.	1:1,000,000 dilution	=	0.000,001 mg.

TABLE 1

Results of tuberculin treatment and dosage used

NUMBER	CLASSIFICATION	PROGNOSIS AT BEGINNING OF TREATMENT	LENGTH OF STAY IN SANATORIUM			DOSE		CONDITION AT DISCHARGE	STATUS THREE TO FOUR YEARS AFTER TREATMENT
			Before treatment	Duration of treatment	After treatment	Minimum	Maximum		
			months	*months*	*months*				
1	M. A.	Fair	42	9	7	0.1 cc. 1:10,000	0.8 cc. undiluted	A. A.	A
2	F. A.	Poor	31	9	1	0.1 cc. 1:10,000	0.7 cc. 1:10	Q	A. A.
3	F. A.	Poor	27	11	17	0.1 cc. 1:10,000	1.0 cc. undiluted	Dead	Dead
4	F. A.	Poor	36	9	6	0.1 cc. 1:10,000	1.0 cc. undiluted	Dead	Dead
5	F. A.	Poor	47	9	46	0.1 cc. 1:10,000	0.1 cc. undiluted	A	A
6	F. A.	Poor	48	9	12	0.1 cc. 1:10,000	0.6 cc. undiluted	Q	Dead
7	F. A.	Fair	54	9	25	0.1 cc. 1:1,000,000	0.8 cc. 1:10	A. A.	A
8	F. A.	Poor	78	5	25	0.1 cc. 1:10,000	0.2 cc. 1:100	A. A.	A
9	M. A.	Fair	48	9	½	0.1 cc. 1:10,000	0.8 cc. undiluted	Improved	A. A.
10	Min.	Fair	19	9	11	0.1 cc. 1:10,000	0.7 cc. undiluted	A. A.	A
11	F. A.	Poor	60	5	48	0.1 cc. 1:10,000	0.2 cc. 1:100	In hospital	Unimproved
12	M. A.	Good	18	6	½	0.1 cc. 1:10,000	0.1 cc. undiluted	Improved	A
13	F. A.	Poor	36	9	48	0.1 cc. 1:10,000	1.0 cc. undiluted	In hospital	Worse
14	F. A.	Poor	84	12	6	0.1 cc. 1:1,000,000	0.5 cc. 1:250,000	Improved	A. A.*
15	Nonpulmonary	Good	11	6	1	0.1 cc. 1:100,000	1.0 cc. undiluted	A. A.	Dead

* This patient has been followed but one year since cessation of tuberculin treatment.

Min. = minimal; M. A. = moderately advanced; F. A. = far advanced; A = arrested; A. A. = apparently arrested; Q = quiescent.

able tuberculosis and all were unable to cope with their disease even after prolonged bed-rest in the sanatorium, augmented by surgical collapse procedures, as will be seen presently. Fourteen had pulmonary tuberculosis, one had tuberculous epididymitis. The clinical course was characterized by one or repeated exacerbations, by persistent lack of improvement or unremitting, slow progression.

Our most extreme case has the following history. In 1925, M. K., a 14 year old girl, was found by clinical, roentgenological and laboratory examination to have bilateral pulmonary tuberculosis without cavitation. Two years of bed-rest at home led to clearing of the lesion on the left side and great improvement of that on the right. She increased her exercise against advice and in 1929 she had far advanced cavernous, bilateral tuberculosis of the lungs and tuberculous laryngitis and enteritis. She was hospitalized at this time under strict sanatorium regimen. The laryngeal and enteric symptoms abated completely. Right artificial pneumothorax was established in March, 1930, and maintained for eight months when adhesive pleuritis intervened. Left pneumothorax was begun in September, 1930, and, two months later, its effectiveness was augmented by open intrapleural pneumonolysis. Improvement followed but, after a year, the girl experienced another exacerbation when on "wheel-chair bathroom privilege." Crushing of the phrenic nerve, temporary improvement, return of tubercle bacilli to the sputum and recrushing of the phrenic nerve featured the next year. In 1933 a new spread appeared for which phrenicectomy was performed. Improvement marked this episode but, after two years of rather strict bed-rest, exercise was begun only to be followed by recurrence of tubercle bacilli in the sputum. Thus, after seven years of sanatorium care and ten years of clinical tuberculosis, this patient still had not controlled her disease.

The other cases varied. Some had an experience almost conparable to this one; some had stationary lesions with occasional positive sputum and no tendency to clear or heal; and some had progressive, unremitting disease.

These 15 patients included 11 women and 4 men whose average age was twenty-one and one-half years, the extremes being twelve and thirty-eight. They had an average of three and one-half years of sanatorium care (one and one-half to seven years) before tuberculin therapy was instituted. They were under close clinical, X-ray and laboratory observation. They were subjected to a program of energetic collapse therapy as well as a strict sanatorium regimen. The treatment consisted of daily, subcutaneous doses of tuberculin given on a scale of increasing amounts and maintained at the patient's limit of tolerance. The doses

did not produce demonstrable focal or general reactions, although local reactions accompanied the full doses. A temperature reaction above 99°F. was regarded as sufficient indication to decrease the succeeding dose. In 5 of the 15 patients injections were either withheld for a few days or the doses reduced at times; in one because of a haemoptysis; in one, four times because the temperature reached 100°F.; in two, six times because of temperature from 99° to 101.2°F. and in another because of slight fever. In one patient the temperature, occasionally 99°F. before treatment, remained at this level at the daily maximum almost regularly during the five months of treatment and ran at a normal level for months thereafter. One desperately ill patient had fever to 102°F., but in this case injections were continued. After weeks of the injection of daily and increasing doses, the febrile reaction subsided.

Twelve patients had their course of treatment started with 0.1 cc. of 1:10,000 dilution; one with a dilution of 1:100,000 and two with 1:1,000,000 which they tolerated without symptoms. The average duration of the treatment was eight and one-half months and at the end of the period 9 of the 15 were receiving undiluted tuberculin daily in doses that varied from 0.1 to 1.0 cc. each. One patient at the end of twelve months of treatment could accept only 0.5 cc. of a dilution of 1:250,000. In all of the patients, as the solution became more concentrated, local reactions occurred, although intracutaneous tuberculin tests, done periodically, showed decreasing skin sensitivity. In none did reaction appear to the injection of 1:1,000 OT which was the original test dose. This represents diminution in degree of sensitiveness, but is no indication that complete desensitization had been accomplished, for 5 of the patients gave small but definite skin reaction to a dose of 1:100 dilution when tested at the end of the course of treatment. Six were negative to this test dose, which represents the highest given. The other 4 were not tested. Experiments in desensitization of tuberculous guinea pigs show the need of daily injection of 1 and often of 2 cc. of undiluted tuberculin to maintain the desensitized state completely. The dose required to produce and maintain this state in man has not been determined. The fact that full doses of undiluted tuberculin produced reaction at the site of injection indicates that the tissues retained a degree of sensitiveness, although the dose which aroused this reaction was relatively great.

As stated above, these patients were selected and treated solely because of their intractable disease. They had experienced exacerbations

from one to five times, had had stationary, nonhealing lesions or had steadily progressive disease. They showed limited exercise tolerance and none seemed able to control his disease even when placed under the favorable circumstance of a well ordered sanatorium regimen and surgical collapse that is adequate in the average run of patients. Table 2 indicates that, in 12 of the 14 pulmonary cases, collapse measures had been employed rather extensively and for relatively long periods. It is quite likely that several of these patients would have weathered the disease without tuberculin. However, attention should be called to the fact that, despite a good sanatorium regimen and a good collapse therapy program, they were prone to relapse or to be stubbornly unresponsive to treatment. This table depicts the leading indications for treatment with tuberculin, as used in this study. We wish to emphasize that this group of 15 patients was given tuberculin as an experiment. We do not advocate routine or frequent use of the drug.

At the beginning of the period of treatment 3 of the 15 were temporarily improved over their admission status, 8 were stationary and 4 were worse than when they had been admitted. At the end of treatment 8 were improved, 5 showed no change, and 2 had lost ground. In the "improved" group only those were included in whom X-ray evidence of receding disease could support clinical evidence and in whom tolerance to moderate exercise was clear.

These patients remained in the sanatorium an average of seventeen and one-half months after treatment (including 2 who have not yet been discharged and one who discontinued the treatment by leaving the sanatorium on her own volition). At discharge one was classified as arrested, 5 as apparently arrested, 2 as quiescent, 3 as improved, 2 died and 2 remain in the hospital and will die. At present, three to four years after cessation of treatment, 7 are arrested, 2 are apparently arrested, 2 are unimproved (still in hospital), and 4 are dead. These data are presented in table 1.

The groups of arrested and apparently arrested cases include a nurse on full-time active duty, 2 women doing office work and 6 women carrying on their household duties at home, one of whom has gone through a pregnancy without effect on the disease. The patient mentioned in the case history belongs to this group. She does light housework and leads a subdued but normal social life. Of the 2 still in the hospital, one has been stationary for ten months and the other is failing slowly. Of the 4

TABLE 2

Collapse treatment used in combination with tuberculin therapy

NUMBER	COLLAPSE BEFORE TUBERCULIN TREATMENT		SPUTUM AT START OF TREATMENT	INDICATIONS FOR TREATMENT	COLLAPSE AFTER TREATMENT	PRESENT STATUS
	Type	Duration				
		months				
1	Phrenic crushing	32	+	Exacerbation, positive sputum on slight exercise	None	A
	Pneumothorax	32			None	A
2	Pneumothorax	30	−	Exacerbation twice, new cavity, slow progression	None	A. A.
	Phrenicectomy	29				
3	Pneumothorax, unsuccessful		+	Progressive disease, two exacerbations on slight exercise	Pneumothorax, unsuccessful	Dead
	Phrenicectomy	23				
4	Pneumothorax, unsuccessful		+	Exacerbation three times, progression	None	Dead
	Phrenicectomy	18				
5	Pneumothorax, unsuccessful		−	Exacerbation, failure to clear or fibrose	Thoracoplasty	A
	Phrenicectomy	20				
6	Pneumothorax	30	−	Exacerbation three times	Contralateral phrenic crushing	Dead
7	Bilateral pneumothorax	53–54	+	Return of positive sputum, exacerbation twice on slight exercise	None	A
8	Three separate thoracoplasty operations (not stages)	60–32	+	Persistent sputum	None	A
9	Pneumothorax	46	−	Failure to improve clinically, failure to clear lesion	None	A. A.
10	Pneumothorax	9	−	Exacerbation on slight exercise	None	A
11	Phrenic crushing	35	+	Frequent positive sputum over long period, X-ray progression, failure to clear or fibrose	Recrushing, contralateral pneumothorax	In hospital
	Pneumothorax	25				
12	None		−	Slow in clearing and fibrosing, occasional positive sputum over long period	None	A

13	Pneumothorax, unsuccessful		+	Exacerbation twice, slow downhill course	Thoracoplasty, six small stages	In hospital
	Phrenicectomy	11				
14	Pneumothorax	81	−	Repeated exacerbations	None	A. A.*
	Contralateral pneumothorax, unsuccessful					
	Pneumonolysis	71				
	Phrenic crushing and recrushing	61–48				
	Phrenicectomy	34				
15	None		−	Epididymectomy, persistent draining sinus	None	Dead

* This patient has been followed but one year since cessation of tuberculin treatment.

who died, 3 succumbed to tuberculosis and one to heart disease. This patient had no indication of cardiac disease at discharge. He died in the street and the coroner diagnosed myocariditis. We discussed the possibility that large doses of protein injected daily may have done damage to the heart as it is known to do experimentally to the kidney of animals (Longcope (3)). But no proof is forthcoming on this point.

In this analysis of results it must be stated that the condition of two of the patients was so poor prior to the tuberculin treatment that thoracoplasty, which they greatly needed, had to be delayed. After the tuberculin treatment the operation was performed. One patient experienced an exacerbation shortly after tuberculin was discontinued. Both have now had thoracoplasty; one is an apparently arrested case, the other is in the hospital, hopeless.

The question of control cases naturally comes up for consideration. General clinical experience with this type of case constitutes a more or less satisfactory control background against which one may evaluate the results presented in this paper. Furthermore, we regarded each patient as a control for himself since he had already had prolonged sanatorium care and vigorous collapse therapy and still was unable to control his disease. However, a study is now in progress which is an elaboration and continuation of the one reported here. In it we are taking for tuberculin treatment alternate patients in the group selected for treatment, leaving every other patient suitable for the treatment as a control case.

The favorable outcome in most of these cases recalls some of the work recorded in the earlier literature. In 1910 Loewenstein (4) treated with tuberculin 682 tuberculous patients under sanatorium conditions and noted that 53 per cent lost tubercle bacilli from the sputum. He placed this figure against his estimated 15 per cent of patients who improved in this way when under similar conditions but without tuberculin. Hamman and Wolman (2) saw many patients lose their reaction to the Pirquet test in the course of treatment with tuberculin, while they were improving.

Recently Fernbach (5) has reported the injection of tuberculin intravenously in children with pulmonary tuberculosis. He contended that the oral administration of potassium iodide increased the tolerance to tuberculin greatly. He was able to abolish the skin reaction to tuberculin in this way and claimed that the sputum became negative and that symptomatic improvement usually followed the course of treatment.

DISCUSSION

In considering the results of this work it seems germane to ask a few questions and discuss the issue briefly from both the theoretical and practical points of view. These questions follow. Were these patients desensitized? This question, now under active study by several observers, is in a state of flux and is subject to considerable deviation from present definition and concept. If one means by desensitization that the administration of tuberculin has obliterated or markedly blunted the capacity of patient or animal to react to ordinary test doses of tuberculin, then these patients were desensitized. If the term indicates total absence of reacting capacity of the skin to concentrated tuberculin, certainly they were not desensitized.

Is the focus more fibrosed as a result of the repeated inflammatory reactions stimulated by injected tuberculin and thus more remote from the body, so that the latter appears less sensitive, at least requires more tuberculin to elicit reaction? Or do repeated injections actually desensitize in the sense of protein desensitization? The work here reported does not elucidate these points.

Do the results reported in this paper have significance? The observations have been made on but a few cases—too few surely to justify conclusions. Besides, these patients had long sanatorium treatment both before and after the period of tuberculin injections. Furthermore, 13 of them had some form of collapse therapy which must be evaluated in summarizing the final results. However, it seems worthy of mention that the number of these patients who recovered completely and were returned to society is large when the prognosis and course are considered. It is logical to inquire whether this method of treatment is very important when the indications are so sharply limited and the occasion for its employment so seldom encountered.

It appears that tuberculin treatment is safe and, within sharp limitations, indicated in the very chronic, "sluggish" type of pulmonary tuberculosis in which the patient reacts but slightly to tuberculin skin test and seems unable to cope adequately with his affection, yet does not succumb, at least not for a long time. The results of this work and the rather scanty work reported within the last two decades would indicate the truth of this deduction.

We wish to emphasize that this study was undertaken solely as an experiment; that we do not recommend the general use of tuberculin

therapy; that we were agreeably surprised at the improvement experienced by more than half of the 15 persons treated; that we believe daily injections of rather rapidly increasing concentration of tuberculin in the chronic, "sluggish" case of pulmonary tuberculosis with low tuberculin sensitivity will lead frequently to distinct improvement; that, if tuberculin is employed at all, the patient should continue under adequate sanatorium and collapse care.

Although these results were better than we had reason to expect, better than such cases experience in the usual course of the disease, we would emphasize the rigid limitations that should always attend the therapeutic use of tuberculin and would raise a warning sign against its use except under the strictest circumstances. These are that: (*1*) tuberculin should be used therapeutically only upon the case that has experienced exacerbation once or several times or has failed to do well under a modern tuberculosis regimen with a thoroughgoing sanatorium and collapse program; (*2*) it should never be used *in lieu* of sanatorium regimen and collapse therapy but always as supplemental to such program; (*3*) full knowledge of the effect tuberculin exerts on the focus of tuberculosis is essential; (*4*) unskilful use of this drug may lead to disaster; (*5*) the number of cases for whom this type of treatment is suitable is very small; (*6*) patients in whom it is used should be in the sanatorium or under close medical supervision; and (*7*) when used in properly selected cases and under these limitations, unusually good results may be expected.

REFERENCES

(1) KOCH, R.: Fortsetzung der Mittheilungen über ein Heilmittel gegen Tuberkulose, Deutsche med. Wchnschr., 1891, *17*, 101.

(2) HAMMAN, L., AND WOLMAN, S.: Tuberculin in diagnosis and treatment, 1912, New York, Appleton.

(3) LONGCOPE, W. T.: The production of experimental nephritis by repeated proteid intoxications, J. Exper. Med., 1913, *18*, 678.

(4) LOEWENSTEIN, E.: Tuberkulinerfolge bei 682 offenen Lungentuberkulosen, Deutsche med. Wchnschr., 1910, *36*, 1654 (quoted from Hamman and Wolman (2)).

(5) FERNBACH, H.: Über langdauernde ohne klinisch wahrnehrnbare Herd- und Allgemeinreaktionen durchgeführte Tuberkulinkuren, etc., Beitr. z. Klin. d. Tuberk., 1932, *81*, 301.

BRONCHIAL CATHETERIZATION[1]

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In the discussion of any method of treatment, it is of interest to note the historical background, the gradual process of improvement and the utilization of previously gained knowledge and experience.

Substances in which iodine occurs in organic combination, such as seaweed or burnt sponge, were employed by Greek and Arabian physicians for numerous diseases. In the Chinese literature of the sixteenth century, burnt sponge is mentioned as a remedy for goitre. Arnold of Villanova (1), in the thirteenth century, recommended it for scrofula. The isolation of iodine was first accomplished by Courtois (2) in 1811. To Laffay (3), in 1901, belongs the credit for perfecting, for the first time, iodized oil. After its appearance in France, iodized oil was administered subcutaneously and intramuscularly for the treatment of such diseases as goitre, asthma and rheumatism. Because it was noted that following these injections, opaque areas appeared on the X-ray film, Siccard and Forestier (4) utilized lipiodol in the X-ray examination of various body cavities, such as the subdural and epidural spaces and the bronchial tubes.

The methods commonly used for bronchography are:

1: Syringe method
2: Passive method
3: Transglottic method
  (a) Intubation method of Iglauer
  (b) Catheter method
4: Subglottic or intercrycoid method
5: Bronchoscopic method

The method I wish to describe in this paper is the transglottic, more especially, the bronchial catheterization method. It is not a means or method of study of the bronchial tree that in any way will supplant bronchoscopy; it is an office procedure, and will open new vistas in the diagnosis and treatment of various bronchopulmonary diseases.

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By means of bronchial catheterization and the instillation of contrast media, we can learn about:

1: Deviation of the trachea and the bronchi from normal position
2: Bronchial stenosis
3: Study of asthma and chronic bronchitis, and its differentiation from bronchiectasis
4: Lung abscess
5: Pulmonary fistula
6: Empyema and bronchial fistula
7: Primary carcinoma of bronchi
8: Tumors of pleura
9: Presence of foreign bodies

By means of this method we can obtain material for bacteriological study from each and every lobe, for the making of autogenous vaccines free from the flora of the upper respiratory tract.

The difficulties first experienced with bronchial catheterization were due to the fact that we used soft rubber catheters. But, even with these catheters, we were always able to fill the lower lobes with contrast media such as lipiodol or campiodol. It was always much easier to delineate the bronchi in the right lower lobe; slightly more difficulty was experienced on the left. The appearance on the market of semirigid, opaque catheters made the technique much more simple and facilitated the catheterization of each and every lobe.[2]

For bronchial catheterization with semirigid catheters, a knowledge of the anatomical considerations of the tracheobronchial tree is of prime importance, especially the directions in which the various bronchi are given off and the distances from the upper teeth to where these bronchi branch off. The distance from the upper teeth to the trachea is 15 cm. The trachea is 12 cm. long. From the carina to the upper lobe bronchus we have 2 cm. The distance from the carina to the right middle lobe bronchus is 5 cm. The right lower lobe bronchus is a continuation of the main stem bronchus. The entrance to the left upper and lower lobe bronchi is about 5 cm. from the carina. If we keep in mind the fact that the right upper lobe bronchus comes off in a lateral direction from the main stem bronchus, and that the right middle lobe bronchus comes off somewhat anteriorly, that on the left we can enter the left upper lobe by directing the catheter in a slightly superior and anterior direction,

[2] George P. Pilling & Son Co., Philadelphia, Pennsylvania.

and if we remember that, by turning the tip of the catheter in a somewhat posterior and inferior direction, we can with ease enter the left lower lobe bronchus, bronchial catheterization becomes a very simple procedure. Even though the distances given above may vary in males, and in females are approximately 2 to 3 cm. less, in reality it is the position and direction of the bronchial catheter that facilitates its entrance into the lobe to be examined.

TECHNIQUE AND ARMAMENTARIUM FOR BRONCHIAL CATHETERIZATION

One needs a good light, a head mirror, a laryngeal mirror, bronchial catheters, a flexible stylet on which to thread the catheters and a DeVilbiss atomizer. The patient and the operator are seated facing each other. The throat is anaesthetized by spraying it with a 2 per cent larocaine or nupercaine solution. With the patient holding his tongue and pulling it gently forward with traction applied by means of his thumb and forefinger on the tip of the tongue, and using a malleable curved tip on the DeVilbiss atomizer, one can spray the pyriform fossa and the epiglottis. When this is accomplished, a glass laryngeal syringe is used and, by means of indirect vision, 2 cc. of a 5 per cent methycaine solution is dropped through the vocal cords and the trachea is anaesthetized. We are now ready to insert the bronchial catheter, which has been threaded on the flexible stylet. With the laryngeal mirror in the left hand, and the catheter in the right, after visualization of the vocal cords, we gradually direct the catheter over the base of the tongue, until the catheter is engaged in the vocal cords. The stylet is then removed from the catheter, and the catheter is further inserted for about 5 cm. By looking at the calibrations on the catheter, which is 40 cm. long, and keeping in mind the distances and directions of the bronchi as they come off from the main stem bronchus, we can enter the right upper lobe by inserting the catheter a distance of 29 cm., and the right middle lobe by inserting the catheter for a distance of 32 cm. The same directions and calibrations apply to the technique of entering other lobes. For the catheterization of the right middle lobe and the right lower lobe and the left lower lobe, we use catheter number one, which is a regular urethral catheter with a Coudé tip. Catheter number two has a curved tip, almost at right angles, and is used for catheterizing the upper lobes. Catheter number three has a still greater curvature at the tip and is used only in deformities and greatly angulated bronchi. To abolish the cough reflex, especially if bronchography is to be done, another 2 cc.

of 5 per cent methycaine is instilled through the tracheal catheter. (Figure 1.)

To obtain material for bacteriological and cytological study the bronchial catheter is removed and the material adherent to the sides of the catheter can be used for making smears or for streaking on culture media. We found, however, that, when the catheter is placed in the lobe under investigation, gentle suction with a luer syringe attached to

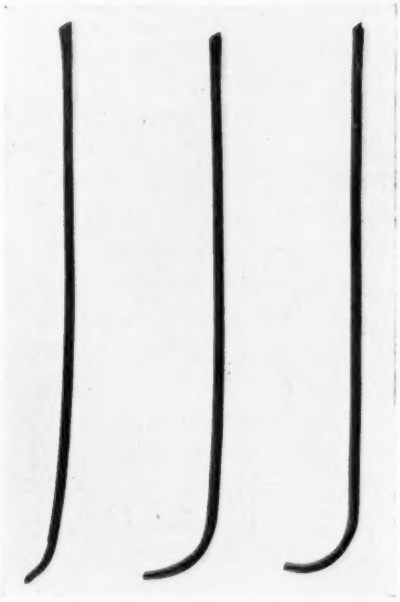


FIG. 1. Catheter no. 1 is used for catheterization of the right middle, the right lower and the left lower lobes. It is a number 20, French, Coudé type, semirigid and opaque to X-rays. Catheter no. 2 has a curved tip, almost at right angles, and is used for catheterizing the upper lobes. Catheter no. 3 has a still greater curvature at the tip and is used only in deformities and in greatly angulated bronchi.

the buccal end of the catheter will frequently suck up sufficient material into the lumen of the catheter. This can be easily washed out of the catheter with sterile saline solution. Material thus obtained in our opinion gives more accurate bacteriological findings and vaccines prepared from this material show a greater variety of organisms.

When bronchography is to be done the lipidol or campiodol is warmed to body temperature and is drawn up in a 10 cc. luer syringe to which a one-way petcock is attached. The petcock is to prevent the spilling of

material and to facilitate its attachment to the catheter. Until the patient is ready to be placed behind the fluoroscope we find it advisable to tape the free end of the catheter to the lower jaw with a piece of adhesive. Under fluoroscopic control the bronchial catheter is gently moved up and down and its position verified. The luer syringe with the iodized oil is attached to the end of the catheter and the oil is instilled with gentle pressure. As a rule 10 cc. of the material is sufficient to map out an important segment of the lung. In 38 cases of bronchography in which careful follow-up work was done, not a single case of iodism developed when the bronchial catheter method was used. It is our belief that the untoward results (5) reported were due to the fact that with other methods used some of the lipiodol probably was swallowed. However, the possibility of allergic reactions to iodine or poppyseed-oil should be considered. As an added precaution against the lodgment of foreign material in the upper respiratory tract following the local anaesthesia of the pharynx and larynx, the patient is cautioned against the use of food or drink for three hours prior to and following bronchial catheterization.

The following cases are cited to show the value of bronchial catheterization as a diagnostic measure.

Case 1: Pulmonary abscess. Mr. H., age 50, was admitted to the Memorial Hospital on February 25, 1938. He presented a toxic appearance, cough was excessive, expectoration profuse and foul, temperature varied from 101° to 103°F. There was a history of a recent attack of influenza, with a subsidence of symptoms for a week prior to admission to the hospital. The onset of symptoms on February 24 was sudden and abrupt, with chills, fever and profuse sweating. Examination revealed dulness throughout the right upper lobe and moist bubbling râles in this area. X-ray examination of the chest showed an area of infiltration in the right upper lobe radiating from the mediastinum. Sputum was negative for tubercle bacilli. On March 1 bronchial catheterization was done, and the instillation of lipiodol showed a suppurative process in the right upper lobe. Following this procedure the bronchial discharge became more copious, but expectoration was brought up with greater ease. Postural drainage was instituted. After a sojourn of two weeks in the hospital, the pulmonary condition cleared up and the patient was discharged as well. (Figures 2, 3 and 4.)

Case 2: Pulmonary haemorrhage following thoracoplasty. Mr. B., age 48, had a fibrocaseous cavitary lesion involving the left pulmonary field sixteen

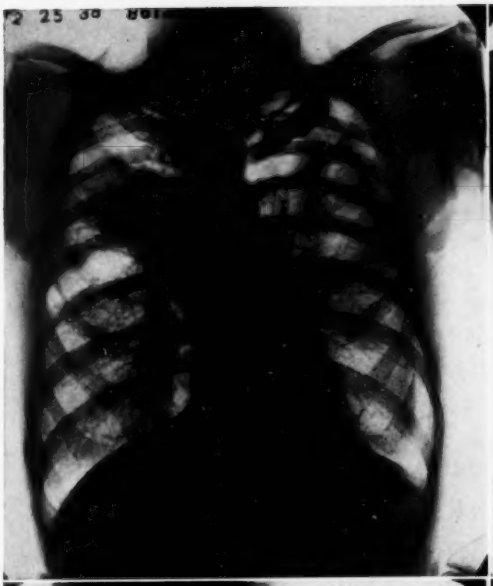


FIG. 2

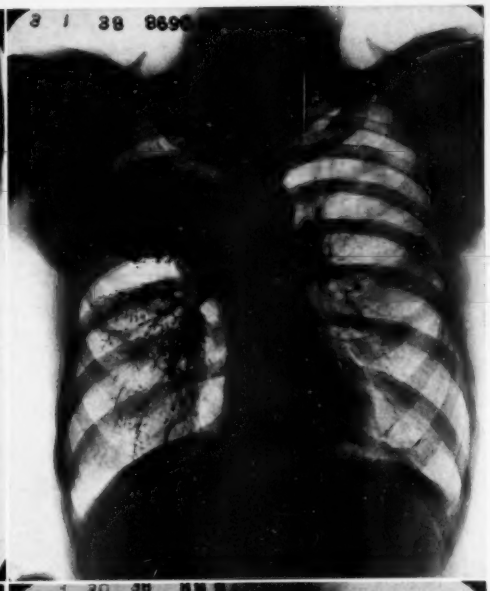


FIG. 3

FIG. 4

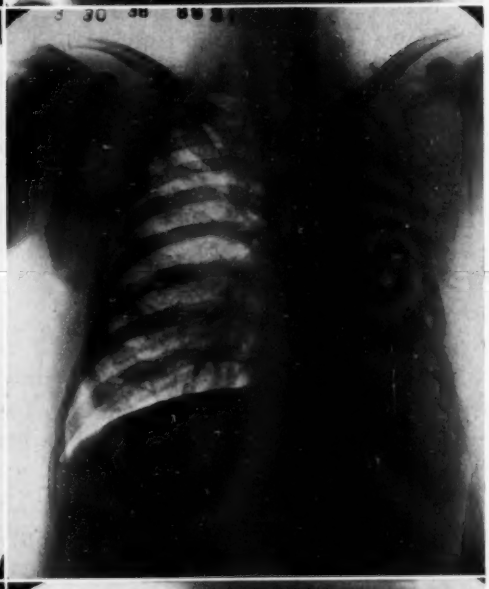


FIG. 5

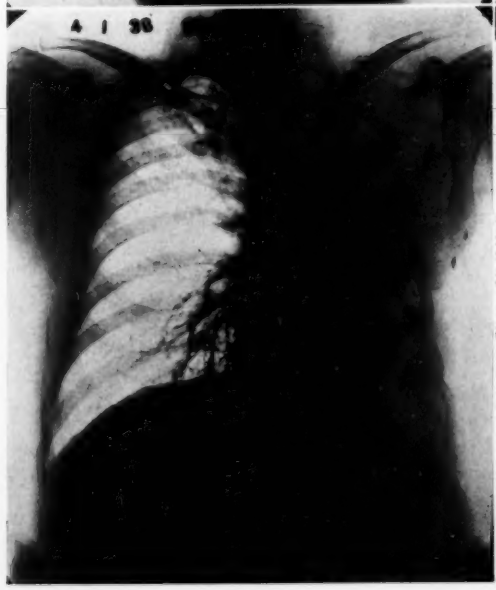


FIG. 6

FIG. 7

years ago, at which time a two-stage thoracoplasty was performed. He has been in fairly good health for many years, his sputum has been repeatedly negative for tubercle bacilli. On or about March 5, 1938, he had a severe pulmonary haemorrhage. Physical examination revealed flatness throughout the left pulmonary area, with coarse bubbling râles from the fourth rib to base anteriorly. An X-ray film of the chest gave little information because of the regenerated ribs and the thickened pleura creating a dense shadow, blocking out the whole left pulmonary area. Physical examination, however, was suggestive of cavitation in the left upper lobe. On April 1, 1938 bronchial catheterization of the left upper and lower lobe was done. The instillation of lipiodol revealed numerous bronchiectatic dilatations throughout the left side and no evidence of cavitation. A small amount of lipiodol instilled in the right lower lobe for comparison showed a normal bronchial tree on the right.

As a result of these studies plans for a revision operation were abandoned. The institution of postural drainage, the aspiration of the mucopurulent bronchial secretions by means of bronchial catheterization followed by the instillation of antiseptics in the bronchiectatic areas brought about marked amelioration in cough, reduction in the amount of expectoration, abatement of fever and a return to gain in weight. Haemoptysis has not recurred. (A paper on the use of metaphen-in-oil 1:5000 for the symptomatic treatments of bronchiectasis is in the process of preparation.) (Figures 5, 6 and 7.)

FIG. 2. Case 1. Shows an incomplete consolidation of the base of the right upper lobe, which appears to originate from the right hilum. The density has a mottled appearance. The lungs appear emphysematous throughout. The above mentioned picture is not characteristic. Possibilities to be considered are unresolved chronic pneumonia; possibly Friedländer's; lung abscess or fungus infection. Sputum was found to be negative for tubercle bacilli and fungi.

FIG. 3. Case 1. The lipiodol mapping of the bronchial tree shows a pooling of the lipiodol in the alveolar structure in the external and posterior aspects of the consolidated and infiltrated lung area. Diagnosis: pulmonary suppuration.

FIG. 4. Case 1. Lateral view showing the pooling of lipiodol in the lower portion of the right upper lobe. Following the bronchial catheterization of the right upper lobe bronchus and the instillation of lipiodol, bronchial discharge became more copious, expectoration was brought up with greater ease, postural drainage was instituted. After a sojourn of two weeks in the hospital, the pulmonary condition cleared up and the patient was discharged. Final diagnosis: pulmonary abscess.

FIG. 5. Case 2. March 30, 1938. There is an old tuberculous process in the right upper lobe. The entire right lung is emphysematous. There is no normal radiable tissue on the left side. The lung is collapsed and the heart and trachea are displaced to the left. The pleura is thickened.

FIG. 6. Case 2. Lipiodol injection shows that there is marked bronchiectasis of the bronchial tree in the left lower lobe. The right lower bronchus is normal. Pulmonary cavities are not evident. The bronchial catheter was left *in situ*. In spite of the marked tortuosity of the bronchi and the displacement of the trachea, the left lower and left upper lobes were catheterized with ease.

FIG. 7. Case 2. A lateral view shows marked bronchiectatic dilatations and the pooling of the lipiodol in the terminal bronchi of the left lower lobe.

Case 3: Bronchiectasis complicating pulmonary tuberculosis. Miss H. was admitted to a sanatorium in Chestnut Hill twelve years ago. At that time she had an acute exudative tuberculous process involving the right upper lobe. Because of the interval of time since her admission, X-ray films taken at the time cannot be located, but throughout her stay at the sanatorium, and she remained there nearly seven years, there have been repeated instances of severe haemoptysis. For the past six or seven years her sputum, examined at frequent intervals, has been repeatedly negative for tubercle bacilli. On

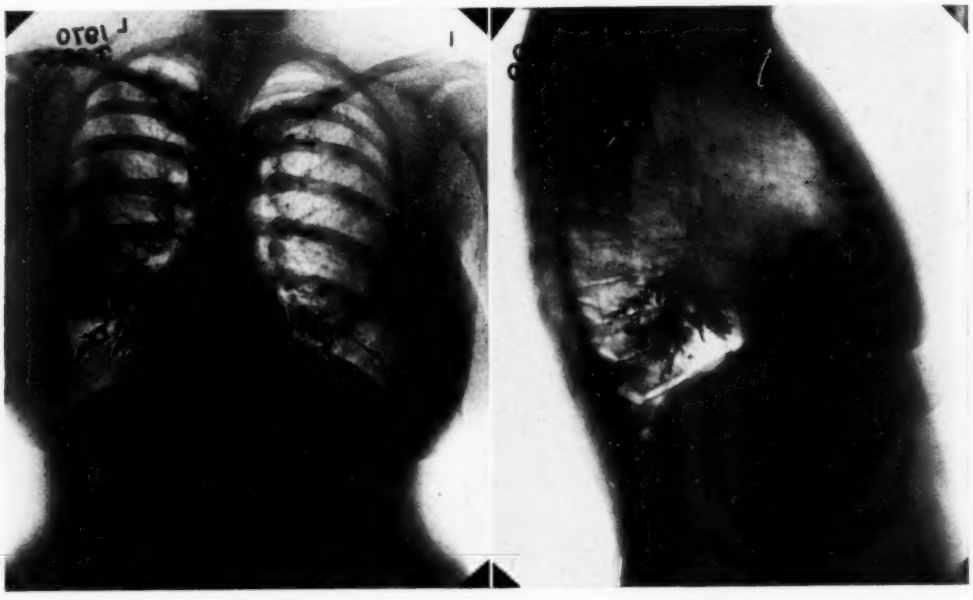


FIG. 8 FIG. 9

FIG. 8. Case 3. Showing marked saccular dilatations of the terminal bronchi, both lower lobes.

FIG. 9. Case 3. A lateral view showing the extensive character of the bronchiectasis.

March 22, 1930, several weeks following a severe pulmonary haemorrhage, lipiodol was instilled in both lower lobes and an X-ray film revealed marked bronchiectatic dilatations in both lower lobes. Assured that her haemorrhages were not due to pulmonary tuberculosis any longer, she left the sanatorium, and since that time she has returned to gainful occupation. The weekly injections of an autogenous vaccine and at monthly intervals bronchial catheterization and the aspiration of the putrid bronchial secretions have kept this patient in fairly good health. Occasionally there occurs slight "streaking." (Figures 8 and 9.)

SUMMARY

1. Bronchial catheterization, together with apparatus and technique, is described. With the development of suitable bronchial catheters and suitable technique, bronchial catheterization has advanced to a place of great importance in the diagnosis and treatment of many bronchopulmonary diseases.

2. Bronchial catheterization is an office procedure, and when supplemented by fluoroscopy and X-ray will aid in the diagnosis of many pulmonary conditions.

3. Bronchial catheterization when properly performed reduces the dangers of iodism to a minimum. The ease with which the bronchial catheter can be placed in the area to be investigated obviates the need for "posturing" the patient or the tilting of the table when upper and middle lung fields are to be studied.

I wish to express my sincere appreciation to Dr. Samuel Alcott Thompson of Sea View Hospital, New York, for his kindly help and suggestions for the improvement in my technique of bronchial catheterization.

I also appreciate the assistance and help of Dr. A. Krieger, Resident Physician, Memorial Hospital, for his selection of cases and coöperation in treating them.

REFERENCES

(1) ARNOLD: Le tresor des pauvres, Lyon Rigaud, 1613.
(2) TOURADE, L. G.: Bernard Courtois et la découverte de l'iode, Paris, Vigor Freres, 1921, p. 127.
(3) LAFFAY, L.: Sur l'huile iodée, biiodurée, et iodobiodurée, Ann. de dermat. et syph., Paris, 1910, *2*, 448.
(4) SICCARD, J. A., AND FORESTIER, J.: The use of lipiodol in diagnosis and treatment, Oxford University Press, London, 1932.
(5) GOLDSTEIN, D. W.: Fatal ioderma following injection of iodized oil for pulmonary diagnosis, J. A. M. A., 1936, *106*, 1659.

PARAVERTEBRAL ASPIRATION OF TUBERCULOUS PSOAS ABSCESS[1]

FREDERICK C. WARRING, JR. AND EDWARD M. KENT

The accepted method of treatment of tuberculous caries of the spine is rest of the affected part. This rest is supplemented by mechanical aids, such as jackets, casts and frames, and by various types of fixation operations designed to give immobility to the diseased area. The healing power of bone invaded by tuberculosis, under this regimen of rest and immobility, is often remarkable.

Healing takes place by new bone formation and ankylosis. At the same time, however, there may be softening and coalescence of tubercles to form a cold abscess in the peripheral bone, and this may progress by contiguity to invade structures surrounding the spine. As the abscess increases in size it forces its way by pressure along the various lines of cleavage of the adjacent anatomy. Such abscess formation occurs in about 25 per cent of the cases of tuberculous spondylitis.

In the case of caries of the twelfth thoracic or any of the lumbar vertebrae the abscess may penetrate downward along the iliac fascia and result in an iliac abscess. Or it may work its way into the sheath of the *quadratus lumborum* and present at Petit's triangle as a lumbar abscess. Very rarely it may become evident as a gluteal abscess. By far the most common occurrence, however, is for the pus to form along the anterolateral aspect of the psoas muscle, to give the familiar bulging psoas abscess.

Once psoas abscess has formed it may do one of three things. (*1*) As the spinal caries heals, it absorbs gradually and uneventfully. (*2*) It increases in size, working its way down the sheath of the muscle, to bulge out under Poupart's ligament on the inner surface of the thigh. (*3*) It can remain stationary for a long period of time, later to absorb or enlarge. If the psoas abscess is absorbing, the lot of the patient and physician is a happy one, and its regression is watched with a feeling of relief. If it extends and presents under the inguinal ligament it must either rupture spontaneously or be aspirated or incised. When rupture has occurred the abscess inevitably becomes secondarily infected and

[1] From the Laurel Heights State Tuberculosis Sanatorium, Shelton, Connecticut.

results in invalidism, a chronic draining sinus, a tendency to development of amyloid disease and an extremely poor prognosis. Aspiration or incision is universally recommended before such an accident occurs, and since none of the standard texts describe the technique of such needling, it is presumed that it is meant to aspirate at the point of swelling on the inner surface of the thigh. When the bulging has thinned the overlying musculature and subcutaneous tissues, the aspiration needle tract may develop into a draining sinus. Likewise secondary infection may set in after incision and drainage.

It seemed reasonable that aspiration of a large psoas abscess could be accomplished through the lumbar muscles. If there were no anatomical obstacles, the abscess could be reached with a long needle, and the thickness of the lower back muscles would reduce the danger of a sinus resulting from the needle track. The only reference to paravertebral aspiration of tuberculous abscesses in the literature is in an article by Koch and Mayer (1). In describing treatment of all types and locations of cold abscesses they mention this procedure briefly but do not outline the technique. We have tried the method on two patients with satisfying results, having aspirated one patient three times and the other twice. The technique and a review of the case histories are herewith presented. This method of aspiration is not set forth as a cure for psoas abscess, but it does appear to have a palliative value. Final absorption of the residual pus with concomitant healing of the spinal caries is the desired end result.

ANATOMY

The psoas muscle (major and minor) arises from the lateral surfaces of the bodies and intervertebral discs of the twelfth thoracic and first four lumbar vertebrae. It converges downward, forward and lateralward to fuse with the iliac muscle and insert in the lesser trocanter of the femur. Abscess forming in any of these five vertebrae and working its way into a head of the muscle usually progresses around the anterior belly of the muscle to establish itself as a bulging mass in the anterolateral aspect of the psoas sheath, just under the peritoneum. An abscess large enough for aspiration, but not yet presenting under the inguinal ligament, will extend about three-fourths of the distance down the length of the muscle. To reach the abscess through the space between the transverse processes of the third and fourth lumbar vertebrae, it is necessary to pass, in their order, through the skin, the subcutaneous tissue, the superficial fascia,

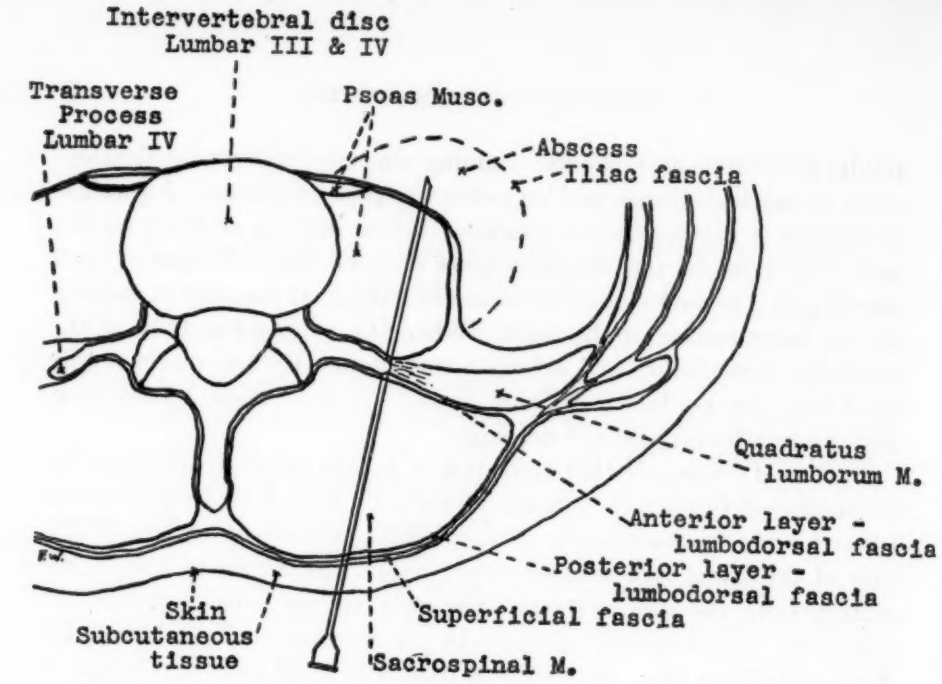


FIG. 1. Transverse section through lumbar muscles at level of transverse process of fourth lumbar vertebra. (After W. Braune.) Position of abscess and direction of aspiration needle are shown.

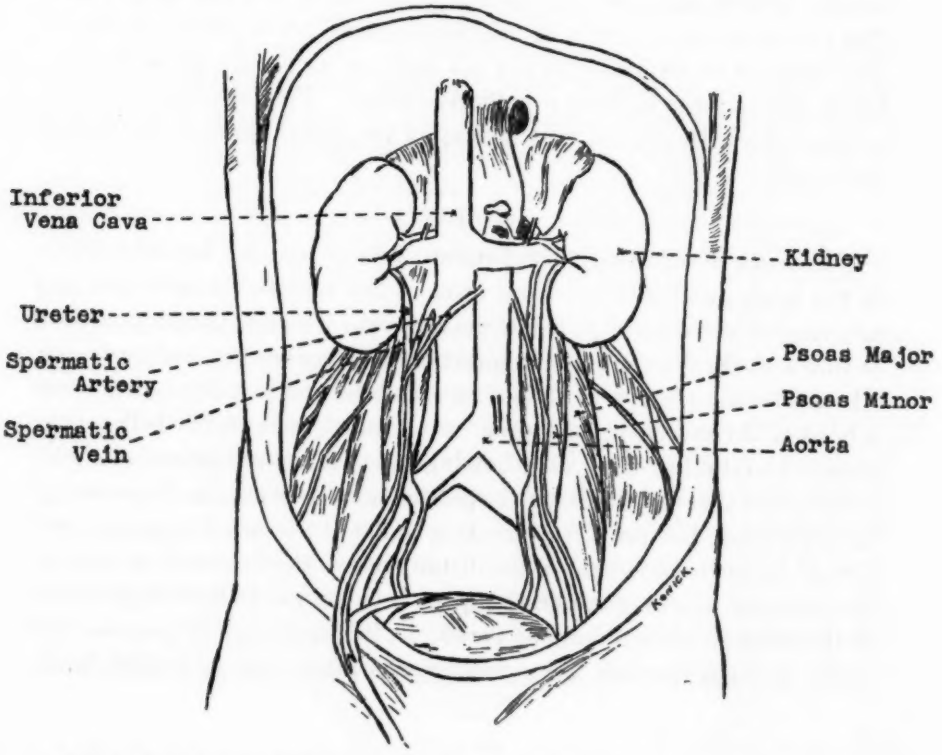


FIG. 2. Anterior view of interior of abdomen. Intestines and omentum have been removed. Structures relative to the psoas muscle are demonstrated.

the posterior layer of the lumbodorsal fascia, the sacrospinal muscle, the anterior layer of the lumbodorsal fascia, the quadratus lumborum muscle and the psoas muscle (figure 1). The abscess usually lies on the anterolateral aspect of the psoas muscle, under the iliac fascia. Its distance from the skin varies roughly from three to five or more inches, depending on the nutrition and the muscular development of the patient.

Lumbar nerves radiate laterally through the muscles, but will not be harmed by careful needling. The lumbar arteries and veins are close to the vertebral bodies and are not endangered. The kidneys are superior to the point of puncture, and are not liable to be perforated. The aorta and vena cava are protected by the vertebrae and their bifurcations are below the path of the needle. On top of the iliac fascia lie the ureter and the spermatic artery and vein. These are in no danger unless the needle is advanced entirely through the abscess and penetrates the iliac fascia (figure 2).

METHOD

The patient is turned on his side, his back toward the operator and the side of the abscess uppermost. The back is comfortably arched forward. The skin of the operative field is cleansed with the usual antiseptics. The skin, subcutaneous tissues and muscles are anaesthetized along the path to be followed by the aspirating needle (*q.v.*) with 2 per cent novocaine, using a long 22 guage needle (figure 3). After anaesthesia is complete a five and one-half inch, fifteen guage needle, attached to a fifty cc. Luer-Lok syringe, is inserted at a point about 5.0 cm. lateralward from the line of the vertebral spinous processes on the side of the abscess and at the level of the space between the third and fourth, or fourth and fifth transverse vertebral processes. The needle is directed slowly inward, parallel to the cross-section of the body and slightly lateralward. Retraction is made on the barrel of the syringe from time to time to determine when the abscess cavity has been reached. When pus enters the syringe, the needle is kept at that position and as much pus as possible is aspirated, without replacing with air. When the abscess pocket has been evacuated, the needle is slowly withdrawn. The needle track is gently massaged for a few seconds and a small sterile dressing applied. The patient may lie on his back following aspiration. With an experience of five aspirations on two patients we have had no difficulty with swelling or reddening at the area of puncture.

FIG. 3

FIG. 4

FIG. 5

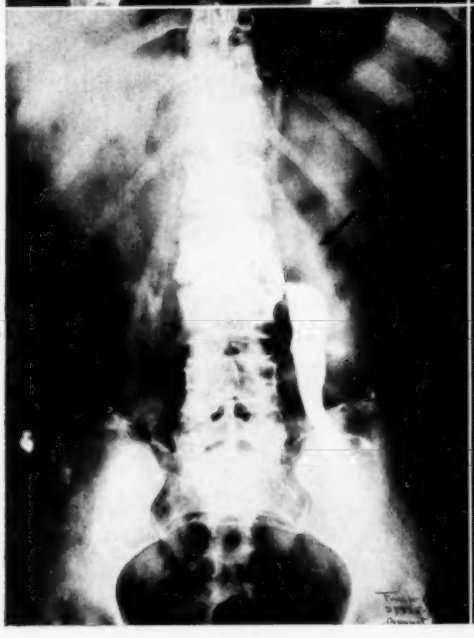


FIG. 6

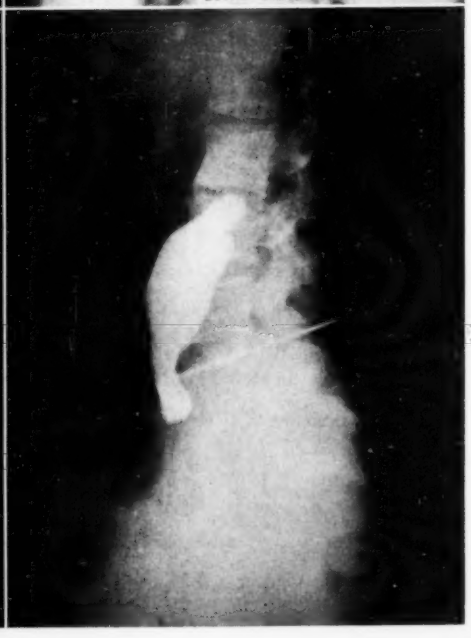


FIG. 7

Case 1: A white male, age 39 years, was under sanatorium care for pulmonary tuberculosis for four years; sputum is now negative. The presence of tuberculous osteitis of the second and third lumbar vertebrae with psoas abscess has been known since June, 1937. Osteosynthesis of the lumbar spine was performed March 14, 1938. Psoas abscess had become of considerable size roentgenologically, but could not be palpated definitely due to obesity of the patient. Persistent pain in the region of the left Poupart's ligament indicated that the suppurating process was pointing in that direction. A paravertebral aspiration of 125 cc. of purulent fluid was performed on May 21, 1938, and the procedure was repeated on August 30, 1938, at which time 200 cc. were obtained. Figure 4 is a roentgenogram of the lumbar vertebrae revealing tuberculous spondylitis centred chiefly in the bodies of the second and third segments. In addition, the left psoas abscess is clearly shown, but its outline has been emphasized by a broken line. Figures 5 and 6 are of the same patient, two weeks after the first aspiration and immediately after the second aspiration, respectively. Distinct, progressive reduction in the size of the abscess mass is clearly shown. To make this more easily apparent, these two films were superimposed upon figure 4, and the unbroken lines of figure 4 are, in effect, the outlines of the abscess after the first and after the second aspiration. When figure 6 was taken, the abscess cavity has been injected with 24 cc. of a radiopaque substance and the result is that the direction and location of the gravitating abscess is clearly indicated. Figure 7 is a lateral view taken at the same time and shows the aspirating needle in place at the level of the fourth lumbar interspace at the time that 200 cc. of pus had been removed and replaced by 24 cc. of radiopaque material. Also shown is the lesion of the vertebrae; the small amount of bone destruction and collapse in this case are obvious. It is worth noting that the opaque material employed in this patient was composed of 10 g. of bismuth subnitrate and 10 g. of iodoform in 100 cc. of sterile paraffin oil. It offers potential therapeutic effect as well as radiographic properties and was decided upon because a similar combination of materials in a petrolatum-wax base has been found efficacious in closing tuberculous sinuses and

FIG. 3. Case 1. Position of the patient and the manner of insertion of the aspiration needle.

FIG. 4. Case 1. The psoas abscess is shown at its maximum extent (broken line). Superimposed in solid lines upon this film are outlines of the same abscess at two later dates (see figures 5 and 6).

FIG. 5. Case 1. The psoas abscess two weeks after first aspiration. It has become reduced in size.

FIG. 6. Case 1. The psoas abscess immediately after second aspiration. It is still further reduced in size, and radiopaque material has been introduced into its cavity.

FIG. 7. Case 1. A lateral view of the abscess immediately after 200 cc. of pus have been replaced by the radiopaque medium. The aspiration needle has been left in place and is clearly seen at the level of the fourth lumbar interspace.

fistulae. A similar use in closed abscess spaces had not been previously attempted by us and we do not yet know what therapeutic effect will be produced in this instance, but absolutely no untoward reaction has resulted.

Figure 8 is shown because it is an intravenous urogram in this patient. The relationships of the urinary tract as it pertains to paravertebral aspiration are well portrayed. The kidney outlines have been emphasized by small arrows

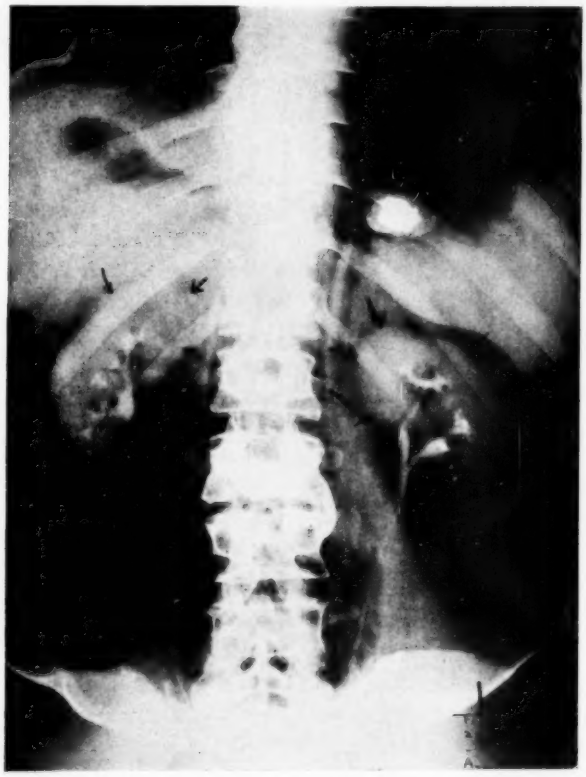


FIG. 8. Intravenous urogram of case 1. The kidney shadows are indicated by small arrows and the abscess by a broken line. The uroselectan fills the kidney pelves and ureters.

and the abscess by a broken line. The uroselectan clearly demonstrates the position of the kidney pelves and the ureters. The impossibility of injury to the kidney and the improbability of ureteral damage is adequately demonstrated in this film.

Case 2: A white male, age 55 years, has been known to have pulmonary tuberculosis for five years and has been under treatment in this institution for two

years. He has also had known tuberculous spondylitis, chiefly involving the third and fourth vertebral bodies, since December, 1937. A large right psoas abscess became easily palpable in January, 1938 and was visualized clearly by X-ray in February, 1938. When dissection of the gravitating mass could be detected below the right Poupart's ligament, paravertebral aspiration of 50 cc. of purulent fluid was performed for diagnosis and as a trial procedure. Ten

FIG. 9. Case 2. Film shows size of psoas abscess at its maximum (broken line). Solid line is superimposed outline of abscess four months later. The bifurcation of the aorta is also outlined to indicate its position.

days later the procedure was repeated with the withdrawal of 400 cc. of pus. Two months later a third similar aspiration yielded 600 cc. of purulent material which was visibly thinner in consistency. Four months after the last aspiration in this patient, the abscess could no longer be palpated. However, an X-ray taken at this time clearly shows the shadow. Figure 9 is the original film in this patient taken preceding the first aspiration; the abscess at its maximum is shown and has been outlined by a broken line. Upon this film

was superimposed the one taken four months after the last evacuation of pus, and the unbroken line inscribed on figure 9 demonstrates that, in this patient too, a reduction in the size of the mass had taken place. This change by X-ray is much less impressive than the clinical findings. Whereas the psoas mass was large and very easily palpable before treatment was begun, it can no longer be palpated at the present time (September, 1938). Attention is called to figure 9 on another score. In this patient, the bifurcation of the aorta was sufficiently calcified to stand out clearly in a stereoroentgenogram. The aortic bifurcation has been outlined in solid lines in figure 9 to show the well protected position occupied by this great vessel.

COMMENT

In commenting on these cases, it seems worth while to consider a few points brought to light above. The first patient was moderately obese, and the posterior abdominal wall was found to be of considerable thickness. A five and one-half inch needle was necessary to reach the pus pocket, whereas the second patient was emaciated and a three and one-half inch needle sufficed. A needle with a calibre of at least 15 gauge was found to be necessary, due to the thickness of the fluid and to the presence of particles of necrotic material in the pus of these abscesses which tend to plug even a needle of this size lumen. Occasionally it is necessary to inject a small amount of air or to insert the stilette to overcome such an obstruction. Case 1 has less far advanced caries of the vertebral bodies than case 2. In spite of this, the size of the abscess in case 1 appears large in X-ray films, but considerably more pus could be aspirated from the smaller appearing abscess. Replacement of 200 cc. of pus in case 1 with only 24 cc. of opaque material seems to outline the cavity rather well. Injection of the abscess with a small amount of bismuth and iodoform in paraffin yielded no untoward results whatever. In no instance was there the slightest suggestion of infection of the needle track, or sinus formation. No systemic reaction of any nature followed this procedure in any instance. In both patients the abscesses are diminishing in size under treatment. While this may be actuated in part or even entirely in patient 1 by the operative immobilization of the vertebrae, such is not the case in patient 2, who is in no condition for surgical intervention, and who steadfastly refuses immobilization on a frame. That anatomical injury can occur as a result of this procedure is quite possible, but it seems that it can only be of consequence if the needle is allowed to pass anteriorly into the peritoneal cavity, or,

much less likely, if ureteral or vascular injury be occasioned in the retroperitoneal space. Paravertebral aspiration can be instituted sufficiently early to forestall gravitation below Poupart's ligament. The level of insertion of the needle can be varied to some extent according to the location of the particular abscess.

SUMMARY

1. A method of aspiration of tuberculous psoas abscesses paravertebrally is described. There is some danger of injury to adjacent anatomical structures involved in the use of this procedure. For this reason paravertebral aspiration should be restricted to that type of abscess which continues to enlarge in spite of adequate treatment of the spinal lesion and which is in danger of rupturing and becoming secondarily infected.

2. The histories of two cases of psoas abscess treated by paravertebral aspiration are presented.

REFERENCE

(1) KOCH, O., AND MAYER, H.: Pathologie, Diagnostik und Therapie des kalten (tuberkulösen) Abscesses, Zentralbl. f. d. ges. Tuberk.-Forsch., 1936–37, *45*, 393.

FACTORS OF HEALING, LATENCY AND PROGRESSION IN PULMONARY TUBERCULOSIS[1,2]

HENRY C. SWEANY

The purpose of this report is not so much to discuss the many theories concerning pathogenesis of tuberculosis, as it is to record and correlate observations in healing and extension of the disease, the better to stabilize principles already established. The clearing of issues in any problem usually results from new facts, and these in turn result from new methods of study, new instruments of precision, or a new combination of these various factors. Inasmuch as there are no new methods or devices, it would be presumptuous to claim anything new. There has been access to an unusual amount of material, however, and perhaps a more complete application of methods with an extension of operative procedure to details not heretofore carried out on a large scale.

To follow the disease tuberculosis in the body and record every change is beyond human possibilities, yet the principal episodes of the struggle of host and parasite may serve as a crude chart of the course taken by the disease in its many manifestations.

Tuberculosis may be viewed as a close combat between two biological agents. Each plays its rôle and modifies the rôle of the other. The host is modified to the status of a diseased patient—the germ to a variegated mixture of bacilli, granular forms and mutants. Some of these factors will now be discussed, beginning with general changes in the host.

Nobody can see tuberculosis in primitive peoples without recognizing the fact that they present a different type of disease than is present in people living in large cities. There is a tendency for the disease to become more generalized like that seen in children. Pinner and Kasper (1), among others, have reported this among American Negroes, but many reports indicate that any primitive race will reveal the same phenomenon

[1] Presented at the 33rd annual meeting of the American Sanatorium Association, Los Angeles, California, June 20, 1938.

[2] From the Research Laboratories of the City of Chicago Municipal Tuberculosis Sanitarium, Chicago, Illinois.

in their native environment. There seems to be a more open lymphatic system, either on a different anatomical basis or due to some unknown immunological factors. Inasmuch as the difference appears to decrease as the races move into the centres of population, it seems that this contact with other people has something to do with altering it. It may be a nonspecific effect due to other antigens. It is known that certain nonspecific antigens act as adjuvants to others in establishing immunity.

Many of the supposed differences, however, may be only apparent. For instance, many primitive peoples may be infected with heavier dosage through ignorance of hygiene, than is ordinarily encountered among civilized peoples, and it may give the appearance of an unusual type of infection. Furthermore, there are deficiencies of diet that may aggravate the disease. Thus far there are no definite facts to explain these differences, but the general variation in aboriginal people is generally accepted.

More important than race is the difference that comes with age. It has long been recognized that the disease is frequently fatal to infants, decreasing in severity to late childhood when there seems to ensue a more benign period. In this "benign age" there seems to be less mortality and active disease, although the infection rate may not be changed. It may be influenced by the thymus or pituitary secretions, but no definite proof is available for such a theory.

As the child passes into puberty, there is apparently a vital change that takes place in the resistance to tuberculosis. At least, there is a pronounced increase in morbidity and mortality. The basic changes that take place in the host at this age are largely of an endocrine nature, resulting in sex development and sudden growth. It may be that these changes offer a better basis for growth of the tubercle bacillus. The newly formed tissues may be more nearly like those of infancy, or the requirements of these rapidly growing tissues may be too great to function adequately in encapsulating tubercle bacilli. Another possibility is that at this age there is a great change in the physical habits of both sexes. Social engagements, irregular hours, dietary fads (especially in girls) are possible contributing factors. In general they have more strenuous habits than adults but are virtually little more than children.

More particularly has attention been focused on girls in puberty in whom the death rate is almost double that of boys at the same age. The temporary physiological unbalance preceding and during the menstrual cycle has long been an established fact and it is possible that in the maturation of a tuberculous lesion these temporary interferences militate

against encapsulation of the bacilli, even though they may only play the proverbial "straw" in breaking the camel's back.

As adult life is reached, however, there seems to be a gradual increase of defensive factors due perhaps to sexual stabilization and a greater ratio of the utilization of factors for maintenance and defense instead of growth. Nonspecific defensive factors must also be thought of in adults. On the other hand there is in general a notable slowing-down of capsule building in adults, which when taken into account with other unfavorable factors, frequently seems to permit the disease to open up and become active. It is doubtful if this factor causes any increase in morbidity. This slowing-down of cell growth with the advancement of age is well described by DuNoüy (2) in the healing of wounds.

As age advances further there are minor periods of stress that seem to enhance the development of the disease. The female in the childbearing period and the male a decade later, with the heavy family responsibilities, seem more prone to become tuberculous. Finally, in old age all defensive factors gradually fail and active tuberculous infection takes on a more progressive character. This state does not always occur at the same age and in the same degree, but a progressive type of tuberculosis in the aged is now a well recognized fact, as studies of Myers and Anderson (3) and others would indicate.

Within the last decade a great deal has been done to show that diet is one of the main bulwarks of defense against most infectious diseases, especially tuberculosis. Of special interest is the work showing that vitamin deficiency leads more quickly to infection. While a balanced mineral and caloric diet has long been known to be important, some of the vitamins, particularly A, D and C, offer shock troops of defense. Especially have Wolbach and Howe (4) shown that vitamin-C deficiency slows down tissue growth by depleting the intercellular cement substance. Such obstacles in the way of tissue growth will tend to enhance the development of tuberculosis as well as other infections.

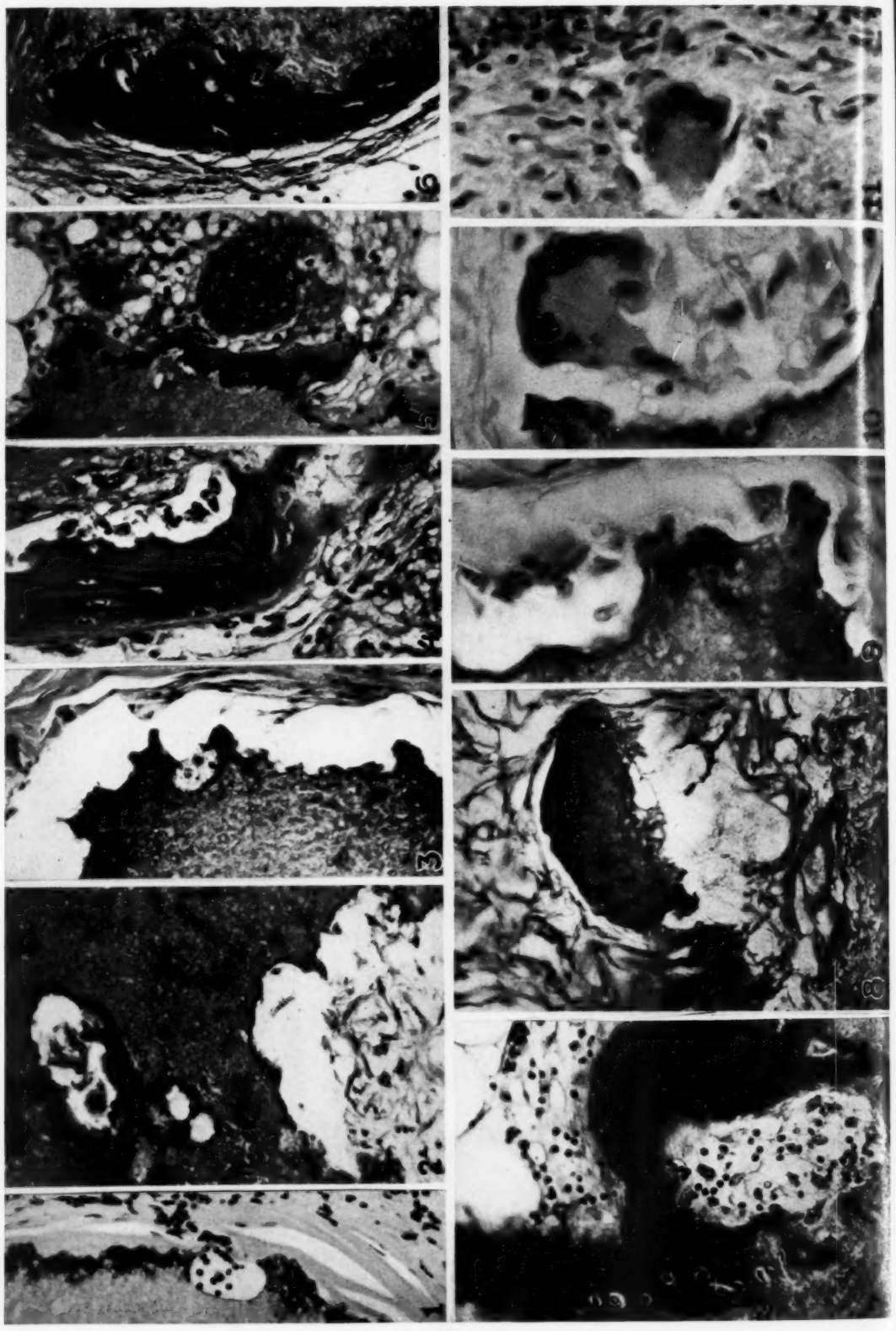
Another important contributing factor in tuberculosis is that of the debilitating diseases. Diabetes and syphilis, when they are acute and untreated, and silicosis at any time seem to enhance the development of tuberculosis. Fatigue, trauma, overwork, worry, severe barometric and meteorological change, etc. may influence the course of the disease during the early phases of tubercle formation. It must be realized also that many of these conditions may be pyramided together to enhance the spread of the disease. Many of these conditions have been included in what Krause (5) has aptly called unfavorable environment.

Although there has not been much said about the changes of the tubercle bacillus itself and its influence on the disease, it is unquestionable that certain strains are more virulent than others, and on the contrary, certain ones have practically no virulence. The original Koch strain, the R1 strain of Trudeau, Calmette's BCG strain, Corper's old human strain, to mention a few, have almost completely lost their virulence after many years on artificial medium. Some strains lose virulence in a remarkably short time. Evanoff and I isolated a bovine strain with very high virulence, but it lost its virulence in less than two years. There were a large number of atypical strains derived from the original material, indicating perhaps that there was an unstable germ plasm in the original strain. Indeed, the changes seem to depend upon a subtle and occult degradation of germ plasm, rather than anything that may be induced at will. Griffith (6), Blacklock (7) and others have made similar observations on variation in virulence. Another confirmation of this is that certain strains seem prone to go into a granular type of degeneration more readily than others, and some of these graunles seem to form mutants of varying degrees of virulence. I am of the opinion that the many changes described as "Much's granules" are mostly degradation changes resulting from unfavorable environment. They are prone to form in any fibroid lesion before arrest. They may be viewed as unstable forms ultimately becoming mutations before complete extinction of life.

It would seem to me, however, that these variants are more important from the standpoint of their possible effect on the capsule of the tubercle than any direct damage to the host. Most of these forms have been found to be harmless, but they may be sufficiently proteolytic to help hasten the softening of the capsule of the tubercle and thus cause a liberation of the forms capable of developing into tubercle bacilli. Bordet cites the fatal effect of the injection of colon bacilli two to three weeks after inoculation with BCG. The effect of mutations and secondary microörganisms may, therefore, be greatly underestimated.

The explanation for many almost miraculous recoveries from tuberculosis may be due to some occult phenomenon in the germ rather than, or as well as, some special defense of the host.

In addition to mutations there is the principle of individual adaptability of bacilli that may, and without doubt does, enter into the problem of tuberculous infection. This has been long recognized with regard to the rapidly growing bacteria since the "passage experiments" of Pasteur, and this possibility must be granted to any living cell including tubercle



bacilli. It is definite, for example, with bovine tubercle bacilli with respect to their ability to grow on glycerine. It has always been a problem to isolate bovine bacilli directly on glycerinated medium, but they may be grown on it after passing through guinea pigs or by gradually adding glycerine. Evanoff and Sweany (8) grew them readily from the original sources on a cream-egg medium without glycerine. After passing them through guinea pigs, however, they grew readily on glycerinated egg medium. There are many similar minor peculiarities that are known by those having much experience with growing tubercle bacilli.

Perhaps the most important evidence of bacterial variation with respect to pathology is the work of Smithburn (9) who produced variants of bacilli by growing them at different pH. The various strains are not only different with respect to "smoothness and roughness" but each type produces a different pathological result in animals. This work, if followed up, may clear up much of the difference in character of tubercles that has heretofore been attributed to some immunological or other factors.

Even if there were no changes within the parasite itself, sheer numbers of them are of tremendous importance. Sewall, de Savitsch and Butler (10) showed experimentally how excessive dosage alone produced a more ulcerative disease than smaller doses. This was also confirmed in the unfortunate Lübeck disaster, as reported by Schürmann. Good evidence of the effect of large dosage is also demonstrated in cases exposed to open

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PLATE 1

FIG. 1. An old encapsulated tubercle showing early resorption with cells resembling lymphocytes. × 80

FIG. 2. Same as fig. 1 except the cells are more like fibroblasts. × 80

FIG. 3. More advanced resorption of a rather old tubercle. Note the phagocytic effect of the special cells. × 80

FIG. 4. Lamellated bone with osteoclastic cells eroding the bone. × 80

FIG. 5. Bone metaplasia in another old tubercle showing bone, marrow and a huge giant cell. × 80

FIG. 6. Bone metaplasia from strands of connective tissue in an old tubercle. × 80

FIG. 7. Transition of fibroblastic cells to bone.

FIG. 8. Early bone formation and transition of reticulum to collagenous fibres to fibrous tissue and bone. Foote's modification of Hortega's silver-carbonate reticulum stain. × 666

FIG. 9. Early bone formation in the tubercle shown in fig. 8. × 666

FIG. 10. Giant cell in a tubercle about twelve years old. × 80

FIG. 11. Same, in the capsule of a "young" tubercle. × 80

(All H. & E. stains except fig. 8.)

cases of tuberculosis in our series where about ten times as many patients break down as in casual contact.

The third and most important phase of this discussion pertains to the two agents resisting each other as a disease. Here, there is the growth of the bacilli within the host and the mobilization of cellular and humoral forces to combat it. During successful healing of a tubercle there is a gradual development of a capsule over the first few years that becomes so heavy that the bacilli are ultimately smothered. In progressive tubercles the process is different. There is an insidious overflowing of bacilli into or beyond the capsule resulting in new colonies. All those familiar with bacteriology know that the cellular wall alone is a poor defense against bacteria. Cells are not bacteria proof, neither are the masses of cells which are formed into a capsule. These two conditions will be described more in detail in turn.

In the former the bacilli locate in the tissues, begin to grow, and then are attacked by the many devices of the body in the battle for supremacy. Acute inflammation, exudation, polymorphonuclear cells, etc.; subacute inflammation, monocytes, lymphocytes, etc.; and chronic inflammation, fibroblasts, fibrosis, etc., are the general order of appearance. In very old tubercles there are vents in the wall that permit capillaries to enter, and in which the walls may be opened up by a lytic action of phagocytic cells (plate 1).

The various changes just described represent the orderly healing of tubercles. Any one or more of the many factors discussed before, however, may conspire to break nature's barriers and loosen the infection around the tubercle. The bacilli may simply outgrow capsule building and result in a spreading process. They may be carried out through the meshes of fibroblasts during early tubercle formation, by monocytes or by tissue fluids. These "overflows" normally occur during a breech in the defense, which may be inherent, traumatic or toxic.

No one can tell at just what phase of tubercle formation the greatest damage may be done, but it seems that the possibilities are greatest during the early months of development when the bacilli are loosely scattered throughout and when breaks in the wall may occur. Bacillus-laden phagocytes may be seen to escape to the surrounding or distant tissues to start new tubercles. It seems also that when the tubercle bacilli once begin to spread there is a tendency for the process to continue even for years and decades. This may be due to an adjustment of the bacilli to their environment that facilitates progression of the lesion.

Sooner or later these "overflowing" bacilli enter alveoli, bronchioli or capillaries and go to near or distant parts of the lung. Perhaps the most common route is by the air channels, because there are not the localizing principles present that are found parenterally. The tubercle becomes larger and finally the bronchi leading out become too large to close, so the result is an open tubercle. This may happen soon or not until years after the infection.

The route pursued by the bacilli in radiating out from an opened lesion is devious. It may produce simply a "colony bud" immediately adjacent to the parent growth but other possibilities must be thought of. Loeschcke (11) has described a route by the bronchioles (fine dissemination) and by the smaller bronchi (coarse dissemination) which he has used to explain the spread from apical lesions. This may even be extended to other localizations than the apex. Lymphatics and blood capillaries are not infrequently the route of infection.

The size of the original focus also has a great deal to do with the result. If it is very large the capsule cannot withstand the growing forces of the bacilli from within. There will be an overflow or a rupture into a bronchus early and it will lead to an open primary focus that may sooner or later result in clinical disease.

Case 1: N. H. (A531) was at death a 19 year old boy who had been exposed to his tuberculous father before two years of age. The child was taken to an orphan asylum at that time and the father died three years later. No illness was complained of until he was seventeen years old when he had a haemorrhage while playing football, after which his disease was discovered. There was an old open primary lesion in the left base behind the heart that communicated with a bronchus. There was a chain of ossified lymph nodes in direct relation with this cavity toward the hilum. There were dry calcifications in the left base, a fibroid cavity in the left upper, and a terminal bronchopneumonia in the whole right lung. (Plate 2.)

After lesions open up, colonies of bacilli may grow luxuriantly on the remaining caseous material that not only endanger others but also the patient himself from autoinfection. Long (12) first clarified this significant phenomenon, although Assmann (13) speaks of a high bacillary content of the ulcerated infiltrate. Approximately half of such excavating caseous lesions are found to contain masses of bacilli.

As mentioned earlier, a high virulence of the parasites may result in a more extensive caseation, ulceration and overflow of the lesion or they

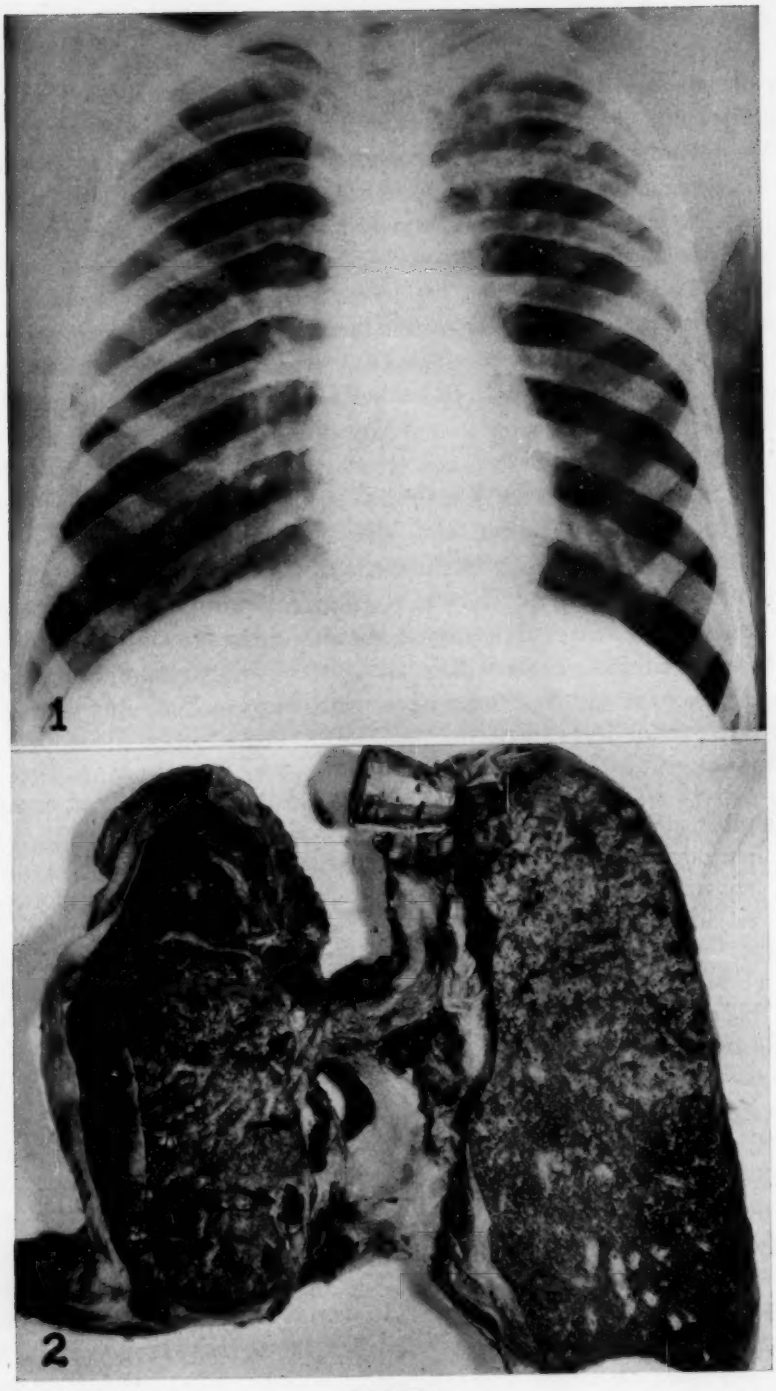

PLATE 2

may metastasize to different places by the bronchi or blood or lymph channels. There may be direct extension through the tissues or a filtering through bronchial walls producing the "hilum catarrh" of Ranke (14). Any large tubercle near a bronchus produces inflammatory effects which extend through the walls into the lumen of the bronchus even without rupturing. The interior of the bronchial wall is permeated with vascular structures, particularly lymphatics which facilitate such spread. The resulting disease may cause occlusion and thus atelectasis.

After the capsules become definitely formed there still are methods of spread that need elaboration. In progressive or even latent tubercles, there frequently appears to be a tendency for the capsule to soften from within. The process seems to begin in the monocytic layer around the caseous centre and spreads outward. At some points it seems to soften more than others. This is such a common observation that it suggests an attempt of the parasite to grow or a local allergy leading to a softening. All the while the process may be aggravated by any one or more of the many variable factors mentioned in the beginning. Sometimes there is a complete break in the wall and a daughter colony or a "colony bud" appears at the side of the parent tubercle. As the tubercles become older, calcification becomes exaggerated in these softened areas. Especially those that have not ruptured. If healing continues, they may be solidly calcified after ten or more years and lose their danger.

The lymph node tubercles may undergo the same changes as the parenchymal lesions. Instead of an overflow into the finer bronchioles, there may be a massive rupture into the larger bronchi with a gross massive dissemination. This method according to Harbitz (15) accounts for about 20 per cent of tuberculous exacerbation.

These changes seem prone to develop with greater facility, if not so frequently, in primary lesions in adults than in children, and herein perhaps lies the explanation of the tendency of adult primary lesions to develop almost directly into the secondary type of disease. The in-

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PLATE 2

FIG. 1. Antemortem X-ray film of case 1. Note cavity in left upper lobe.

FIG. 2. Sagittal section posterior to the trachea (from behind) revealing an old fibroid cavity behind the heart that perpetuated the infection from childhood on; an ossified complex toward the hilum; fibroid cavity in the left upper lobe; and an acinonodose (bronchogenic spread) in the right lung.

fections in adults may range from extensive pneumonic lesions with only abortive lymph node components to small lesions that would not appear to be of any significance at all. While most small infections are of no consequence, the size does not seem to prevent the "accidents." The course is commonly about as follows: From one of several foci, the "break" occurs, an overflow results, then a nodular reinfection or infiltrate appears. This infiltrate then commonly ruptures into bronchi, and less frequently into blood vessels, to result in what is recongized as clinical disease. Barring tuberculosis of the aged, there are about as many deaths in young adults as in all other age groups put together. There seem to be more factors causing awakening of the latency at this than any other time, and the cases infected at this age run a shorter course. The average period of latency is eighteen years in those infected under five years, but it diminishes to two and one-half years for those infected in the teen age period. In each group there is an unknown number of patients recovering entirely, but there also seems to be a quota in each that goes on to insidious spread by one or more of the methods listed before and perhaps influenced by the numerous other factors. In spite of the fact that many young adults die of tuberculosis, many infections also heal without disease.

In late tubercle formation there are also changes that are interesting if not significant in the spread of the disease. By studying tubercles of different ages it is found that giant cells are frequently found in the monocytic layer. They are frequent in young tubercles and may be seen in tubercles up to the twelve year type. Of course, these may be only foreign body giant cells, but the suspicion is strong that many are due to living parasites. It is comprehensible that parasites may survive for years within a tubercle. They have been kept alive by Corper and Cohn (16) for nearly fourteen years in culture flasks, and I have grown bacilli from apparently well encapsulated primary tubercles up to the seven year type. There does not seem to be any reason, therefore, why tubercle bacilli may not live for ten years or longer in tubercles, since streptococci and the parasites of malaria, syphilis and of other diseases may live for similar periods.

Furthermore, there is the natural disintegration of the tubercle that seems to be entirely unrelated to the parasites. Although there is the possibility that this opening up of the capsule may liberate germs, I have never observed a direct extension of the disease as a result of these

regressive disintegrations. It is a possibility, however, if old latent parasites chance to be present at the time of opening up of the tubercle.

Thus far little has been said of the effect of hypersensitiveness and desensitization on the spread of the disease. I have purposely left it to the last because it is the least tangible of all evidence. It is not to be interpreted as indicating a lack of importance. The more obvious features have been placed first. It is my opinion that this phenomenon has more to do with the disease after the latency has ended and clinical disease has begun. It has been long recognized that it plays a big rôle in "secondary" or "reinfection" types of disease by leading to a greater reaction at the site of infection. Certain authors, such as Krause and Willis (17), have ascribed much of the protection afforded by an infection to allergy as well as exudative character. It is Myers's (18) belief that much of the violent reactions and exudation of secondary lesions are due to a hyperallergy. Rich and McCordock (19) are of the opinion that allergy is principally destructive and that immunity is entirely separate from allergy. There is still much uncertainty about the problem, but the matter has been well stated by Bronfenbrenner (20) who compares allergy to a stove that furnishes warmth when the fire is left in the fire box, but, if allowed to spread beyond it, will destroy the building. As yet there does not seem to be need to invoke the many complicated phases of allergy introduced by Hayek (21) or even Ranke (14), but the general principles are genuine and important.

Although there are many possibilities for the action of allergy in active clinical disease there may also be some in preclinical disease. One is the focal necrosis or caseation inside the capsules where an increased metabolism and liberation of antigen from the parasite may affect the sensititized cells around. Another is the general late caseation that spreads outward from the centre and (sometimes suddenly) causes an overflow through the capsule.

The question of allergy must be considered in both these conditions. In following the development of a primary process on X-ray films, the lymph nodes toward the hilum may be seen to enlarge several weeks after the parenchymal primary lesion has been formed. By this time the cells of the lymph node could very well be allergic and under certain circumstances of dosage, could soften and slough. The respective rôles of allergy and living bacilli, however, in these conditions is quite vague.

In later disease, as shown by Willis and others (22), the gradual absorption of tuberculin seems to cause a desensitization and a recession of allergy. The same desensitization may apply to other proteins as well. There is, therefore, added a complication to the process which is genuine, but most difficult at present to resolve.

Little has been said, and perhaps little can be said, about the influence of immunity. Protection due to infection is definite, but the mechanism of the process is still obscure and until tangible evidence is produced to show that immunity is demonstrable apart from allergy, it has no place in this discussion.

After considering the many major and minor episodes that lead to disease extension within the lung itself, equally important is the spread of disease beyond the lungs. While all extrapulmonary disease cannot be described, the principal mechanisms may be pointed out and from this the various conditions arising may be better understood.

There are three possible routes of infection outside the lungs, namely, the lymphatic route to the lungs from an extrapulmonary infection (usually primary); the general arterial circulation from the left heart, originating from an infection in pulmonary ulcers; and a return to the lungs by the general venous circulation from some extrapulmonary focus (usually a secondary). These will be described in turn.

The lymphatic route is that usually pursued by extrapulmonary primary lesions. The course is to the main lymphatic ducts to the left subclavian vein and then to the lungs. It may and frequently does originate from a primary in the lungs and returns again to the lungs. This may be well illustrated by citing a case of a primary gastrointestinal infection that spread to the lungs producing a *localized* miliary tuberculosis in the lungs. The degree of involvement may range all the way from a few *bilateral* apical tubercles to a complete dissemination throughout. These types are perhaps part at least of what Delarue has called "cold" miliary tuberculosis. (See plates 3, 4 and 5.)

Case 2: T. C. (A1057) an 11 year old boy whose maternal grandfather died of "rheumatism" twenty-four years ago and whose maternal grandmother died of tuberculosis three years before he was born. There was no other his-

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PLATE 3

FIG. 1. Antemortem X-ray film of case 2 showing miliary tuberculosis.
FIG. 2. Postmortem X-ray film of same. There are no calcified primary lesions.

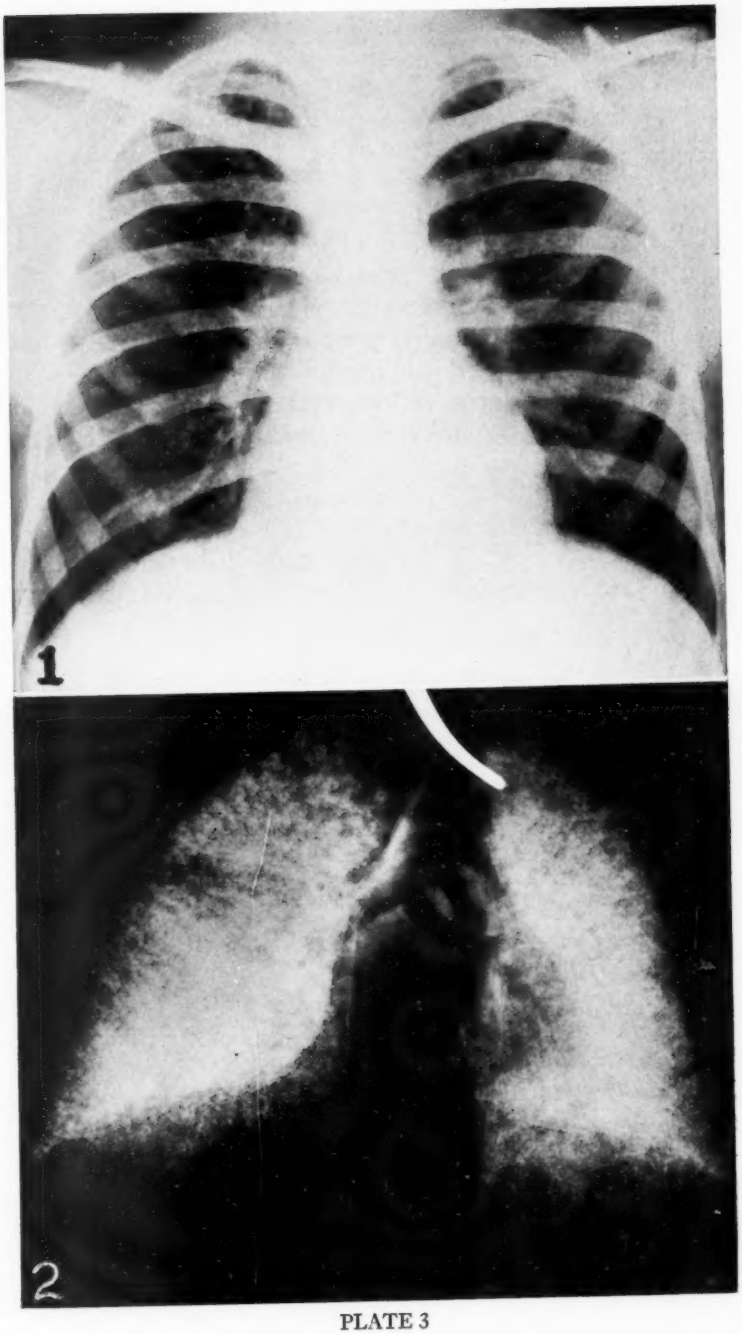

PLATE 3

tory of tuberculosis. His own mother, however, was "ill with arthritis." An infection was acquired about five years before the patient's death, because the lesions were of that age type. As this coincides with the mother's arthritis, it is possible that the infection was obtained from her.

The clinical history was only of one and a half years' duration. It began with a swelling below the left ear, due to tuberculous lymph nodes. There was an ulcer of the left tonsil. The tuberculin test was positive. The X-ray revealed a questionable "miliary tuberculosis" of the lungs. The blood revealed a mild anaemia, slight leucopenia and an unfavorable Schilling index. One month before death the sputum was found positive for tubercle bacilli.

The postmortem revealed a primary tuberculosis in the left cervical region and at two places in the ileum with primary calcifications in the wall of the bowel and in the regional lymph nodes. There were huge ulcers in the bowel at these places showing that the primary lesions had remained open. The age type of all calcified lesions ranged from a four to six year type. There was an evenly distributed miliary tuberculosis in the lungs, more marked in the upper portions and decreasing in size in the lower parts. There were a very few small miliary tubercles in the spleen and liver, that were thought to be a terminal process. Amyloid was present in the liver and spleen. (Plates 3, 4 and 5.)

Comment: This was a *local* miliary tuberculosis in the lungs due to a lymphogenous seeding by way of the thoracic duct. The few miliary tubercules in the spleen and liver may have been due to an overflow from the lungs.

Contrasting this with a generalized miliary tuberculosis, there is a vast difference in the origin. In general dissemination the major circulation is penetrated, most commonly in the pulmonary veins or venules.

Case 3: H. C. (A606) was a 6 year old boy whose aunt had tuberculosis; the child visited her occasionally since early childhood. The first sign of disease was noticed four and a half years before death when the child contracted a "cold" and "bronchitis." At a year and a half before death he developed a right-sided otitis media. He began to lose weight six months before death, at which time symptoms of a generalized miliary tuberculosis appeared. The

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PLATE 4

FIG. 1. Sagittal section through the main bronchi of case 2.
FIG. 2. X-ray film of left side of neck showing primary calcifications.
FIG. 3. Calcification in a mesenteric node.
FIG. 4. Calcifications in the wall of the ileum.

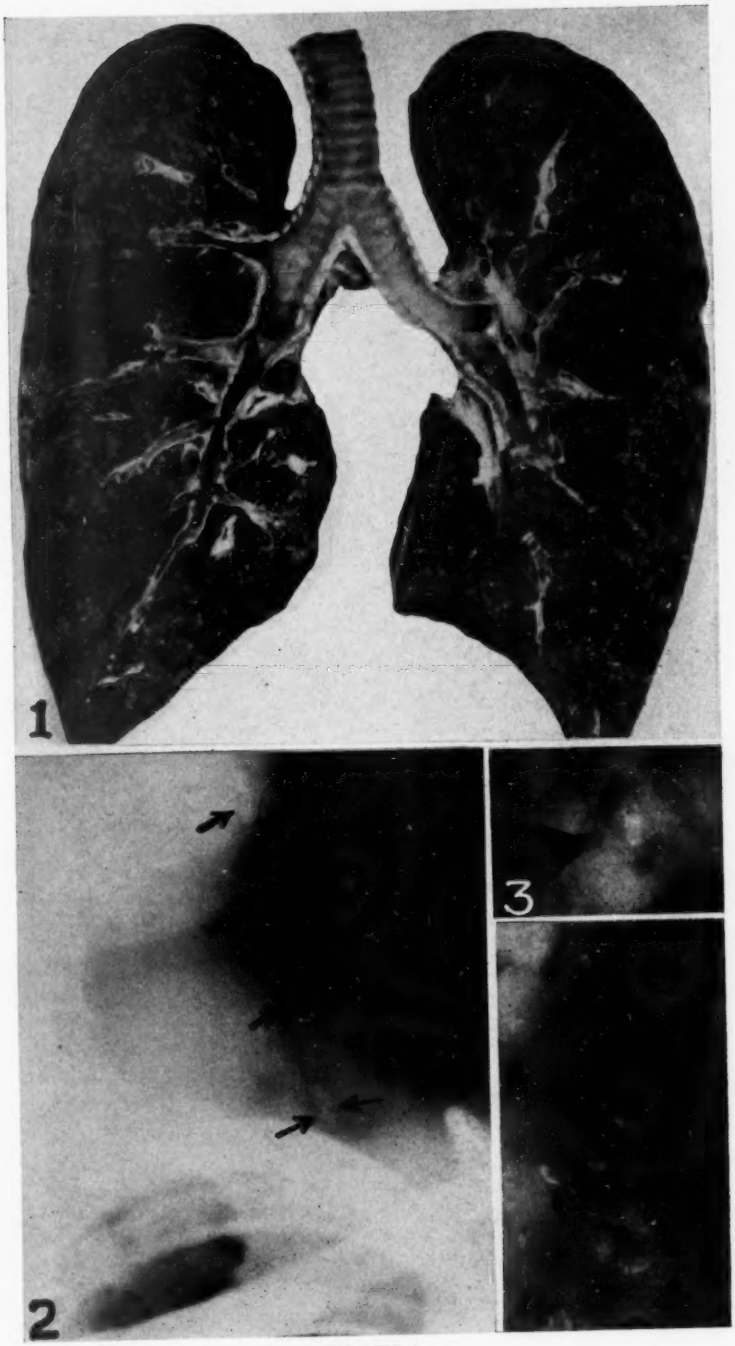
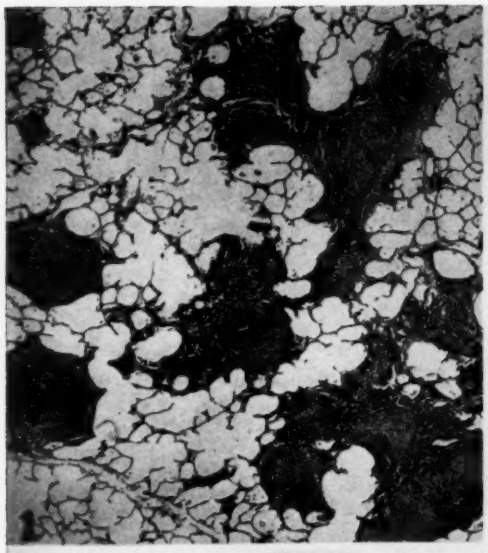
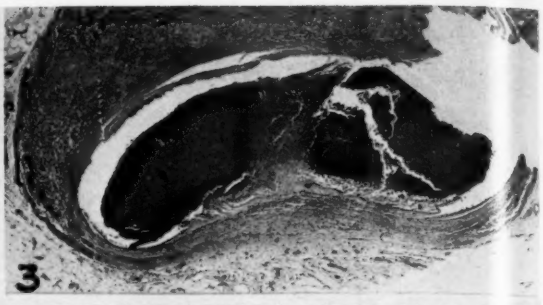


PLATE 4





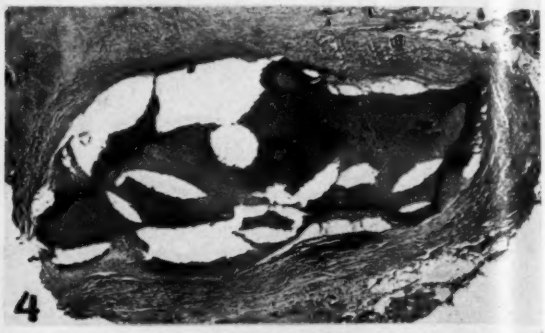


PLATE 5

infection must have occurred when the patient was between one and one-half and four years old, and it was between two and four and a half years old. The bronchitis was probably the onset four and one-half years before death.

There was a typical primary tuberculous complex at the left base anteriorly and at the hilum. The inferior and superior tracheobronchial nodes and the left tracheal nodes were also involved. The age of the tubercles was of a three to five year type.

Other findings were severe tuberculous enteritis and generalized miliary tuberculosis. The latter resulted from a tubercle in a pulmonary lymph node that grew through the wall of a left pulmonary vein producing a pendulous mass in the vein. There was a generalized spread throughout the body, producing about 100 tubercles per square centimetre of a lung section, 20 tubercles per square centimetre of a section of the spleen, 10 in the liver, 5 in the adrenal, 2 in the kidney, 1 in the thyroid, but none in the heart muscle.

In addition to the main penetration of the pulmonary vein there were many giant cells found entering the smaller capillaries both arterial and venous. In direct relation to the arterial capillaries were found an excessive number of miliary tubercles in the region supplied.

Toward the apices the progress of the dissemination was more marked than toward the base. Numerous "overflows" into the finer bronchioles were observed, and descending capillary bronchitis was the result. (Plates 6, 7 and 8.)

This is in marked contrast to the preceding case where the miliary dissemination was confined principally to the lung.

The return of bacilli to the lungs by way of the veins and pulmonary arteries is difficult to demonstrate as a major episode. It happens no doubt as a minor phase of other episodes, and occasionally I have seen extrapulmonary tubercles penetrate veins, particularly in lymph nodes and once, already reported (23), in a tuberculosis of the prostate, but it is not commonly seen. When it does happen there is usually a concomitant generalization that overlaps the process.

The many extrapulmonary localizations of disease are too varied and numerous to describe in this type of report. It must be kept in mind that when tubercle bacilli once enter the body the possibilities of reimplantation are almost endless. The primary lesions, particularly in

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PLATE 5

FIG. 1. Photomicrograph of a *strictly localized* miliary tuberculosis in the lung. × 16
FIG. 2. One of several calcified tubercles in the wall of the ileum. × 22
FIGS. 3, 4 & 5. Calcified tubercles in the mesenteric nodes. × 16

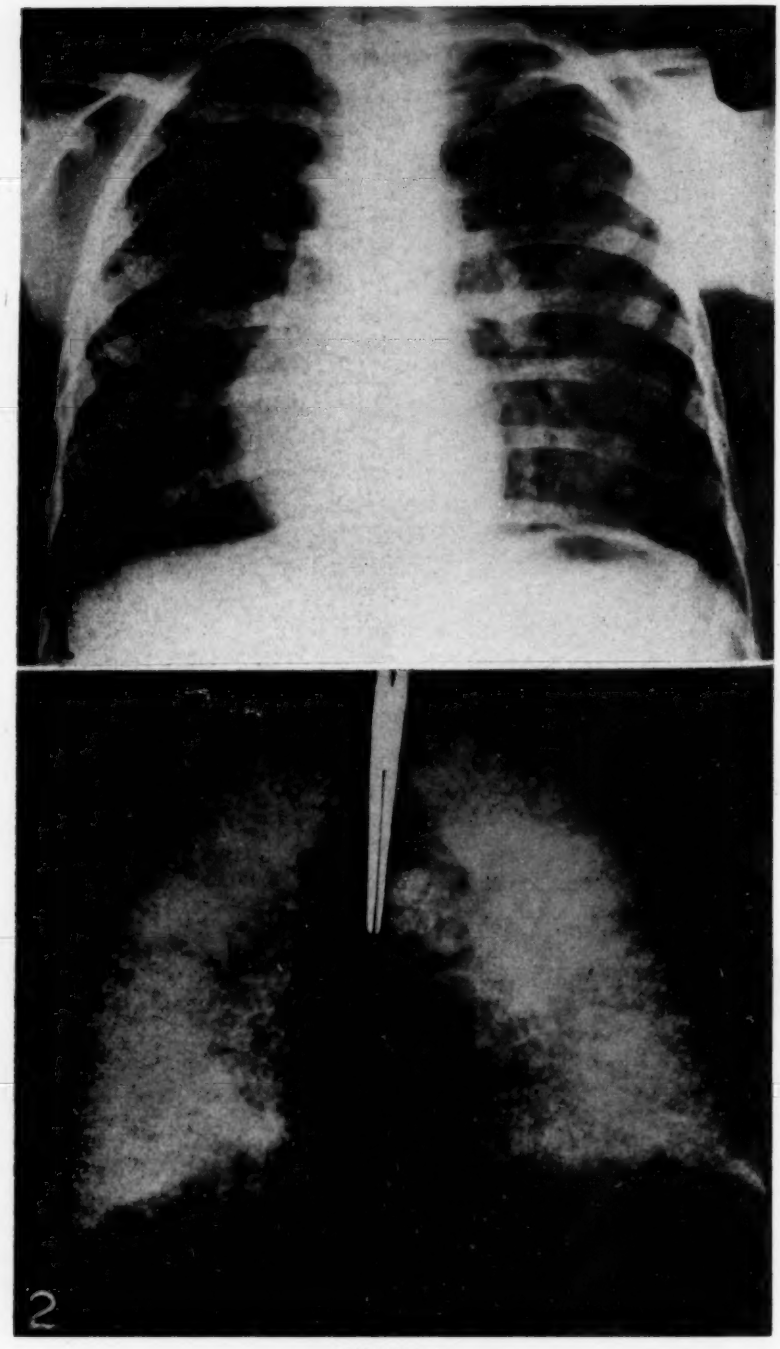

PLATE 6

FIG. 1. Antemortem X-ray film of case 3. Similar in appearance to case 2.

FIG. 2. Similar to case 2 except that there is an early primary calcification in the left lower lobe and hilum.

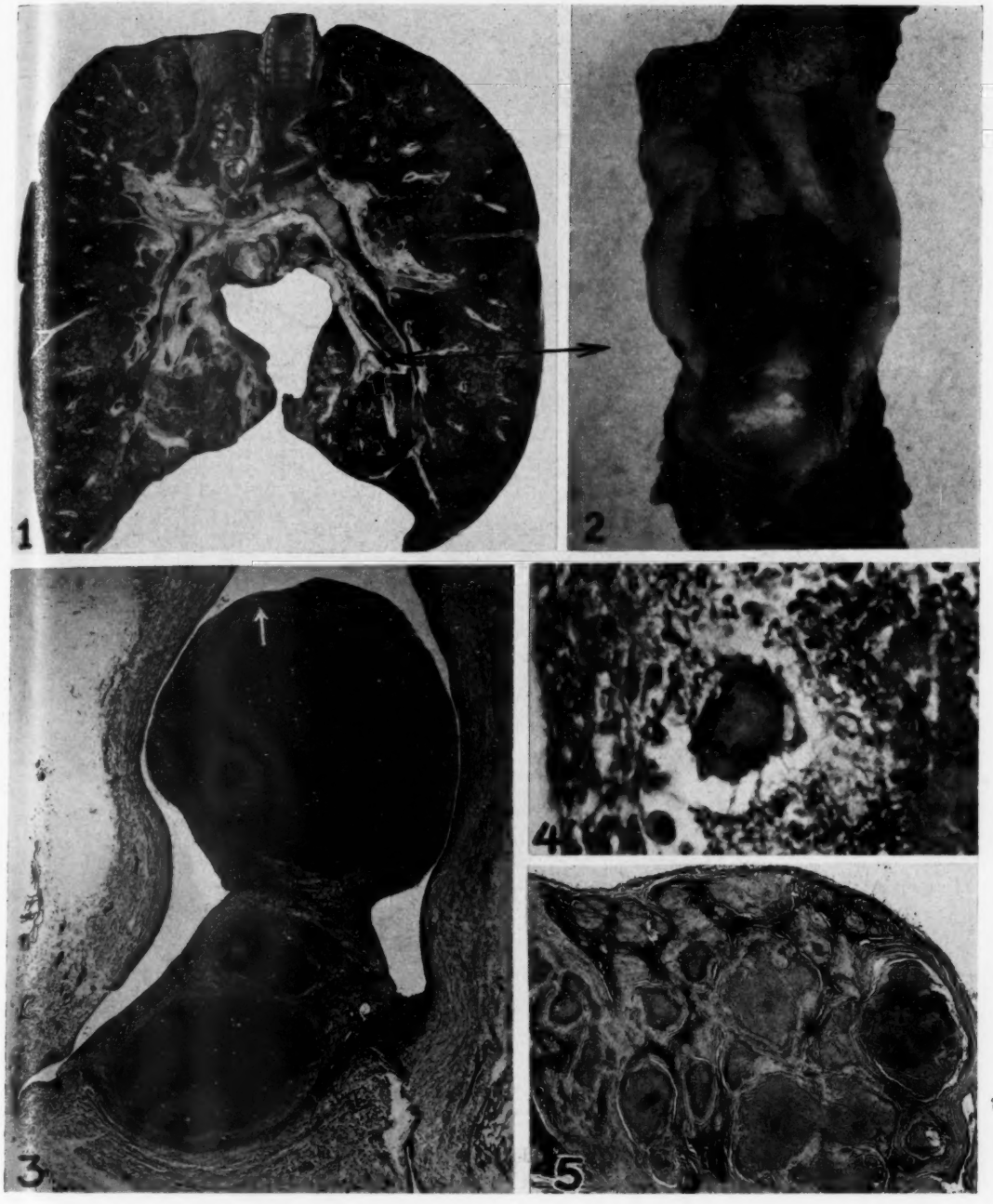

PLATE 7

FIG. 1. Sagittal section (posterior view) of lung. Note left sided primary lesion and the pendulous tubercle, indicated by the arrows, in pulmonary vein on right side.

FIG. 2. Pendulous tubercle shown in the vessel. Enlarged 6 ×

FIG. 3. Sagittal microscopical section of the same. × 13.3

FIG. 4. A giant cell in the margin of figure 3. × 290

FIG. 5. Photomicrograph of primary focus in the hilar lymph node. × 6.3. This is a four year process.

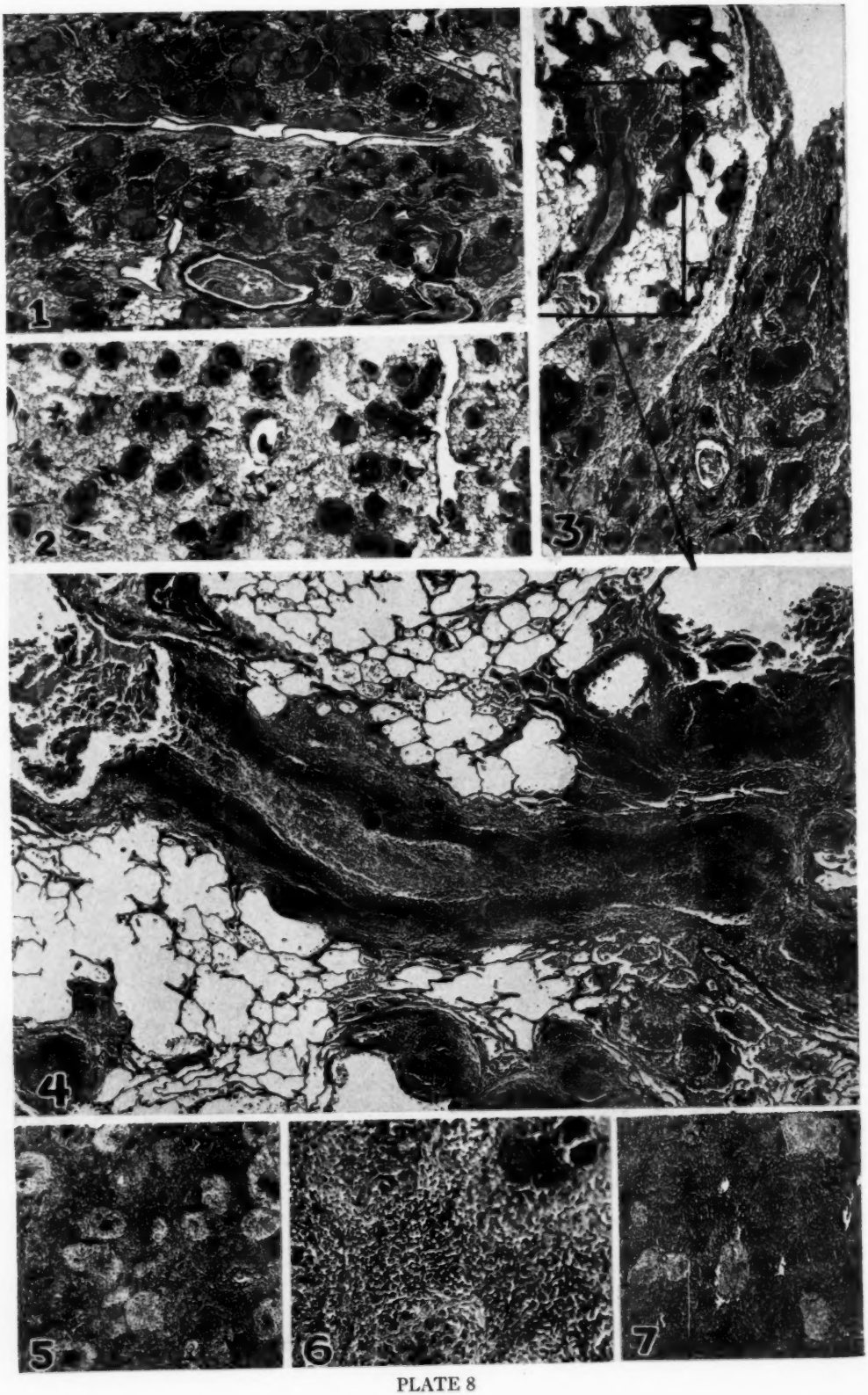

PLATE 8

the young, produce showers of bacilli in the general circulation, most of which die off, but many produce lesions that may heal or may produce exacerbations later in bones, joints, kidneys or meninges. It is evident also from some of the preceding illustrations that some of the lesions of the primary infection present episodes that spread bacilli in the tissues or in the blood-stream in limited showers as each capillary is penetrated. When the capillary is closed the particular episode is ended. The limited showers may localize in any organ and produce disease. In the terminal stages of the disease, showers from many sources may occur that localize in various organs and produce individual or multiple lesions. The recent work of Duchaine (24) in rabbits has shown the mechanism of these haematogenous localizations.

In progressive lesions, there are numerous episodes as the spreading tubercles encroach upon the various channels in the tissues. If they penetrate the air passages or lymphatics they are confined to the lungs, but if they penetrate pulmonary veins they lead to systemic generalization.

If the infection has arisen from exogenous sources, it may follow the same courses after it becomes localized in the lung.

SUMMARY

The progress of tuberculosis in the body is determined by many definite and variable episodes and many more indefinite or contributing factors involving both host and parasite. It is a "battle on many fronts" with the weakest points giving way before the "enemy's attack." All classifications, from Bard and Piéry down to the present, bear witness to the fact that tuberculosis has many end results leading to many diverse classifications. So many end results must necessarily be caused by as many antecendent factors, obviously too varied for consideration in this work; but suggestions for a better understanding of some of the early phases and of the *modus operandi* of the processes are offered. No view of pathogenesis can be complete without the consideration of age, race,

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PLATE 8

FIG. 1. Densely seeded tubercles in lung. Note giant cell in small pulmonary vein. × 6
FIG. 2. Miliary tubercles in section of lung base. × 6
FIG. 3. A section from apex. Note "capillary bronchitis." × 5.3
FIG. 4. Enlargement of the caseous bronchiole. × 17.3
FIG. 5. Miliary tubercles in spleen. × 16.5
FIG. 6. Same as fig. 5. Enlarged 75 ×
FIG. 7. Miliary tubercles in the liver. × 16.5

sex, etc. of the host and of the many variations of the parasite. The manifold evolutionary or accidental episodes of the lesions must be considered (open primary foci, ruptured lymph nodes, etc.) and these must all be interwoven with the intricate and little understood development and recession of hypersentiveness (allergy) and of desensitization and immunity.

REFERENCES

(1) Pinner, M., and Kasper, J. A.: Pathological peculiarities of tuberculosis in the American Negro, Am. Rev. Tuberc., 1932, *26*, 463.

(2) DuNoüy, L. P.: Biological time, New York, The Macmillan Co., 1937.

(3) Myers, J. A., and Anderson, H. R.: Significance of tuberculosis among the aged, Am. Rev. Tuberc., 1930, *21*, 541.

(4) Wolbach, S. B., and Howe, P. R.: Intercellular substances in experimental scorbutus, Arch. Path., 1926, *1*, 1; Soc. Exper. Biol. & Med., 1924, *22*, 400.

(5) Krause, A. K.: Environment and resistance in tuberculosis, Harvey Lecture, 1923.

(6) Griffith, A. S.: Bovine tubercle bacillus in human tuberculosis, Brit. M. J., 1932, *2*, 501.

(7) Blacklock, J. W. S.: Tuberculous disease in children, London, 1932.

(8) Evanoff, M., and Sweany, H. C.: Culturing bovine tubercle bacilli, Am. Rev. Tuberc., 1929, *20*, 227.

(9) Smithburn, K. C.: Virulence of bovine tubercle bacilli, Ibid., 1937, *36*, 637.

(10) Sewall, H., de Savitsch, E., and Butler, C.: Nodules of experimental tuberculosis in the guinea pig and their relations to immunity, Ibid., 1932, *26*, 1.

(11) Loeschcke, H.: Development, cicatrization and reactivation of pulmonary tuberculosis in adults, Beitr. z. Klin. d. Tuberk., 1928, *68*, 251.

(12) Long, E. R.: From pathology to epidemiology in tuberculosis, J. A. M. A., 1935, *104*, 1883.

(13) Assmann, H.: Über die infraclaviculären Infiltrationen im Beginn der Lungentuberkulose von jugendlichen Erwachsenen, Klin. Wchnschr., 1927, *6*, 2128.

(14) Ranke, K. E.: Ausgewählte Schriften zur Tuberkulosepathologie, Berlin, 1928.

(15) Harbitz, F.: Untersuchungen über die Häufigkeit, Lokalisation und Ausbreitungswege der Tuberkulose, Christiania, 1905.

(16) Corper, H. J., and Cohn, M. L.: Viability and virulence of old cultures of tubercle bacilli, Am. Rev. Tuberc., 1933, *28*, 856.

(17) Krause, A. K. and Willis, H. S.: The influence of frequently repeated reinfections on allergy and immunity in tuberculosis, Am. Rev. Tuberc., 1926, *14*, 316.

(18) Myers, J. A., Harrington, F. E., Stewart, C. A., and Wulff, M.: First-infection-type tuberculosis, Am. Rev. Tuberc. 1935, *32*, 631.

(19) Rich, A. R., and McCordock, H. A.: An enquiry concerning the rôle of allergy, immunity and other factors of importance in the pathogenesis of human tuberculosis, Bull. Johns Hopkins Hosp., 1929, *44*, 273.

(20) Bronfenbrenner, J.: Allergic state and its relation to hypersensitiveness and resistance, Am. Rev. Tuberc., 1937, *36*, 293.

(21) Hayek, H.: Referred to by P. Huebschmann in his Pathologische Anatomie der Tuberkulose, Berlin, 1928, p. 116.

(22) Willis, H. S., Woodruff, C. E., Kelly, R. G., and Voldrich, M.: Allergic and desensitized guinea pigs, Am. Rev. Tuberc., 1938, *38*, 10.

(23) Sweany, H. C.: Primary tuberculosis of the prostate, J. Urol., 1933, *29*, 217.

(24) Duchaine, J. P.: Tuberculous bacillaemia in rabbits, Am. Rev. Tuberc., 1938, *37*, 507, 520.

RESISTANCE TO TUBERCULOSIS[1]

I. Factors Associated with the Bacteria

KENNETH C. SMITHBURN

Until such time as investigation shall uncover highly efficient methods for the specific prevention of tuberculosis, there will be need of an understanding of all the forces which have a part in influencing the course of the disease, either in man or in animals. This need is particularly apparent to workers in experimental tuberculosis, as the ordinarily slow course of the disease makes investigations expensive and progress slow. The prolonged course of the disease may also allow intercurrent factors to play an important rôle, adding to the difficulty of interpretation of results. The need for more precise methods in investigation of tuberculosis was emphasized by Berg who proposed a statistical interpretation of data (1) and, reliant thereon, a standard method for testing vaccines (2). Such procedures would, no doubt, be a step in advance but do not take into account certain factors associated with the mycobacteria, and others associated with the host, which may influence the course of the disease. Toward the end of elucidating some of the latter factors, the experiments reported in this and the succeeding paper were carried out.

The most obvious factors associated with the bacteria which might be expected to influence resistance are virulence of the organisms, the number of them gaining access to the body, and the route by which they enter the body and, consequent thereon, the location of the lesions which they produce. For instance, a diffuse, generalized tuberculous meningitis is associated with early death, whereas an equal mass of tuberculous lesions in the lung or spleen would not cause death except by extension of the process, which would require more time. Medlar and Sasano (3), Winn and Petroff (4), and Steeken, Oatway and Petroff (5) have demonstrated differences in the lesions produced by attenuated and by virulent mycobacteria and we have confirmed and extended these observations (6, 7, 8). As result of these studies, it is now clear that attenuated mycobacteria, when introduced into a susceptible host, induce circumscribed "hard" tubercles which may regress, or which progress slowly, causing death

[1] From the Laboratories of The Rockefeller Institute for Medical Research, New York City.

only after a prolonged period (7); but virulent organisms introduced into a susceptible host produce complex lesions which advance rapidly, are markedly prone to necrosis and caseation, and lead to the early death of the host (6, 7).

The intracerebral route of inoculation was used many years ago by Manwaring (9) and more recently and extensively by Feldman (10, 11) and Boquet and Broca (12) in their studies on tuberculosis. We (6, 13) have shown that this method is most useful in quantitative studies on tuberculosis. In the present investigations we have employed the technique previously described (13) in studies on host and parasite factors as they are related to resistance to the disease.

MATERIALS AND METHODS

Animals: The rabbits used in these experiments were, for the most part, lilac-English hybrids bred in the Rockefeller Institute. Individuals of both sexes were employed. All were young adults and each animal was caged separately. The guinea pigs were, for the most part, albino male animals of streptococcus-free stock bred in this Institute. A few guinea pigs from commercial stock were used. Four guinea pigs of one sex were usually caged together. All animals were isolated prior to use and observed for evidence of disease. Only vigorous, healthy animals were employed. Whenever direct comparisons of virulence or titrations of virulence were done, animals of comparable sex, age and weight were selected so that groups would be as nearly as possible alike.

Cultures: The bacteria were grown on Corper's (14) glycerolated egg-yolk medium, adjusted to pH 6.8, except as specifically indicated in individual experiments. Vigorously growing cultures, usually about three weeks old, were used. Suspensions were prepared by grinding a weighed quantity of bacteria, freshly removed from the medium, in a mortar with sterile saline solution so that 1 cc. of suspension contained 1 mg. of bacteria. From this suspension dilutions were prepared to contain the desired quantity of organisms. Considerable care was taken in the preparation of suspensions to avoid clumping and to insure uniform dispersion of bacteria. This was best accomplished by grinding the bacteria first without fluid, then with drop-wise addition of fluid, until several cubic centimetres had been added. The use of phosphate buffers or of a solution of sodium taurocholate did not seem to facilitate dispersion

of the organisms. Suspensions were used promptly after preparation. The strains of bacteria will be described under individual experiments.

Inoculations: Intravenous or subcutaneous inoculations were made in the usual manner. Intracerebral inoculations were made by the technique described previously (13), ether or seconal[2] being used for anaesthesia. The latter was administered intraperitoneally in a quantity equal to 20 mg. per kilogram of body weight. With seconal the anaesthesia obtained within twenty minutes following administration was quite adequate for the operative procedure and no postanaesthetic, pulmonary complications were encountered. With two technical assistants, and by employing seconal for anaesthesia, it was found possible to inoculate animals intracerebrally at the rate of about one per minute.

Measurement of results: Largely we have employed the survival time following inoculation as the measure of infectivity and of virulence. When direct comparisons were made on the survival of different groups of animals, the significance of the result was determined by ascertaining the difference in their mean survival and dividing by the probable error of that difference. The result was not considered certainly significant unless the difference was three or more times its own probable error.

Postmortem examinations were done on all animals. Individuals dying from extraneous cause were discarded from further consideration In many instances microscopical surveys of the lesions were also made.

STUDIES ON NORMAL VARIATIONS IN SURVIVAL AFTER INOCULATION OF A STANDARD DOSE OF ORGANISMS AND TITRATION OF THE MINIMAL LETHAL DOSE OF TUBERCLE BACILLI

In the experiment which follows it may be observed that, with intracerebral inoculation, significant differences in survival do not occur when various groups of carefully selected animals are inoculated with the same dose of the same suspension of organisms. The second half of the experiment was done to determine the end-point of virulence for a given strain, that is, the minimal infective dose.

Five groups each of four male, albino guinea pigs, varying in individual weight from 300 g. to 400 g. and in group weight from 1,420 to 1,440 g., were inoculated intracerebrally with highly virulent bovine tubercle bacilli, strain 39. Each animal was inoculated with the same dose,

[2] Sodium Propyl-methyl-carbinyl Allyl Barbiturate, Lilly, generously supplied by Eli Lilly and Company, through the courtesy of Dr. G. F. Kempf, Indianapolis City Hospital.

TABLE 1

Normal variations in survival after intracerebral inoculation of 0.000,01 mg. bovine tubercle bacilli—animals of similar weight

NUMBER OF ANIMALS	MEAN WEIGHT	SURVIVAL	
		Mean	PE_M
	g.	*days*	*days*
4	355	27.75	1.62
4	360	25.75	4.42
4	355	26.0	1.33
4	357	28.25	2.10
4	355	27.25	1.30
4	487	23.75	3.80

TABLE 2

Variations in survival time due to variations in the dose of organisms injected intracerebrally, and titration of the end-point of infectivity

ANIMAL NUMBER	INOCULATION DOSE	SURVIVED	MEAN SURVIVAL
	mg.	*days*	*days*
R 5821*	0.000,01	25	23.75 ± 3.80
R 5822		39	
R 5823		14	
R 5824		17	
R 5825	0.000,001	23	33.75 ± 3.34
R 5826		40	
R 5827		28	
R 5828		44	
R 5829	0.000,000,1	47	35.25 ± 2.95
R 5830		35	
R 5831		33	
R 5832		26	
R 5833	0.000,000,01	S^1	
R 5834		S^2	
R 5835		214	
R 5836		83	

S^1 = Sacrificed 216th day. No tuberculosis.

S^2 = Sacrificed 216th day. Low grade tuberculosis.

* These are serial numbers used in this laboratory over a period of years.

0.000,01 mg., of the same suspension of organisms within the same hour. All succumbed to tuberculosis. Table 1 shows that significant

differences in mean survival did not occur among the five groups. A sixth group of slightly older and heavier guinea pigs from the experiment which follows were inoculated at the same time with the same dose of organisms as the five preceding groups. The data on their survival time are included at the bottom of table 1.

In addition to the above, four groups each of four male, albino guinea pigs of individual weights varying between 440 g. and 530 g., and of group weights varying between 1,890 g. and 1,960 g., were inoculated intracerebrally, each group with different doses of the highly virulent bovine strain 39. Each animal of the first group received 0.000,01 mg., each of the second received 0.000,001 mg., each of the third received 0.000,000,1 mg., and each animal of the fourth group received 0.000,000,01 mg. The results of the latter inoculations are shown in table 2. It will be seen from the data (table 2) that every animal receiving a dose of 0.000,000,1 mg. or more succumbed to the disease. Of the four receiving a dose of 0.000,000,01 mg., two succumbed and two survived; and in one survivor there was unmistakable tuberculosis. The animal which succumbed on the 214th day (table 2) exhibited clinical evidence of disease (loss of weight and paralysis of an extremity) as early as the sixty-first day, was alternately better, then worse, and at autopsy revealed a large, sclerosed tubercle at the base of the brain, together with minor metastatic lesions.

From this experiment it was learned that, with intracerebral inoculation of carefully selected groups of animals, significant differences in survival do not occur in groups receiving the same dose of a given suspension; but significant differences in survival time do occur among groups inoculated with different doses. Finally, it was found that the minimal lethal dose of the bovine strain 39 was between 0.000,000,1 mg. and 0.000,000,01 mg. (see comment in Discussion).

STUDIES ON THE RELATION BETWEEN VIRULENCE OF MYCOBACTERIA AND THE RESISTANCE OF THE HOST

Two female New Zeland red rabbits, weighing 2,720 g. and 2,800 g. respectively, were inoculated intravenously with 0.01 mg. each of bovine tubercle bacilli, strain B39, isolated by the late Dr. Theobald Smith. One rabbit, R 5183,[3] received organisms of a line attenuated by repeated

[3] These are serial numbers used in this laboratory over a period of years.

subcultivation on medium adjusted to pH 6.0 (6), while the other, R 5184, received organisms of a line, the virulence of which was maintained through repeated subcultivation on medium adjusted to pH 6.8 (6). X-ray films were made of the thorax of each animal (to show the lung fields) once weekly during the eight weeks following inoculation, and of

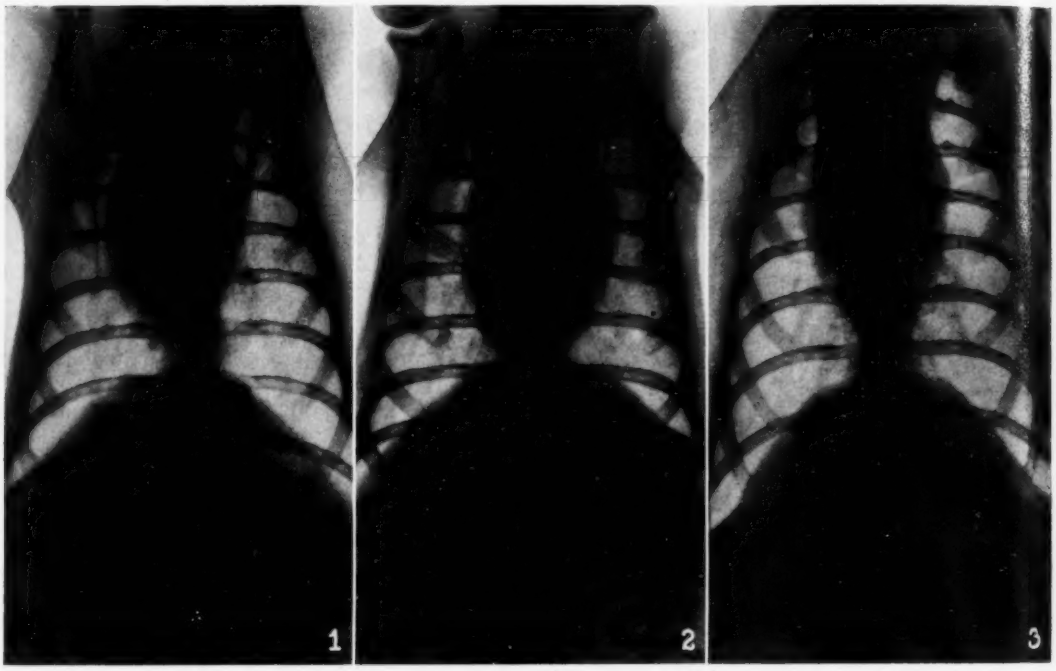

FIG. 1. Roentgenogram of lungs of rabbit R 5183 taken thirty days after inoculation with the attenuated line of bovine strain 39. The lung fields are relatively clear.

FIG. 2. Roentgenogram of lungs of rabbit R 5183 taken fifty-eight days after inoculation with the attenuated organisms. The lung fields still show little abnormality.

FIG. 3. Roentgenogram of lungs of rabbit R 5183 taken one hundred ninety-seven days following inoculation with attenuated organisms. The lungs still are quite clear.

the surviving animal, R 5183, at monthly intervals for five months additional.

The lung fields of the two animals remained relatively clear during three weeks. In the films taken at the end of four weeks (figure 1), the lungs of R 5183 remained clear, while definite miliary shadows were seen in the lower lobes of R 5184 (figure 4), and there was some haziness of the line of the diaphragm. During the next four weeks the lungs of R 5183 remained clear (figure 2), while the infiltration in the lungs of R

5184 became more pronounced (figure 5) and the plates showed relatively little air-bearing tissue in the lungs. Up to this time the rabbit receiving attenuated organisms, R 5183, had gained 410 g., while R 5184, inoculated with the same dose of fully virulent organisms, had just maintained its preinoculation weight. During the next week the latter lost 600 g. and succumbed on the sixty-fifth day following inoculation. At autopsy massive tuberculous lesions were found, the lungs corresponding to 4.48

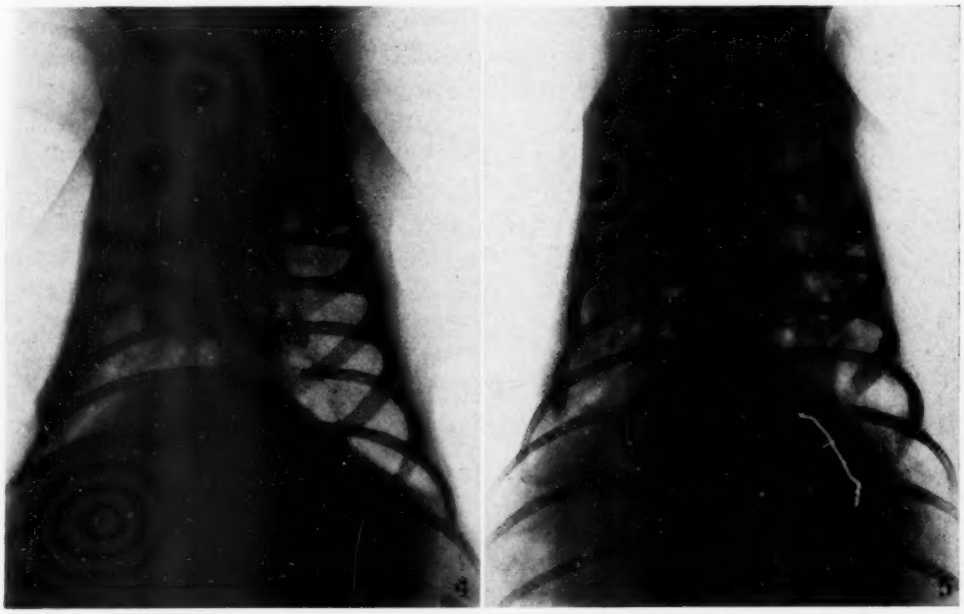

FIG. 4. Roentgenogram of lungs of rabbit R 5184 taken thirty days after inoculation with the highly virulent line of bovine strain 39. The lungs show extensive infiltrations, and the line of the diaphragm is fuzzy.

FIG. 5. Roentgenogram of lungs of rabbit R 5184 taken fifty-eight days after inoculation with highly virulent organisms. The lung fields show massive infiltration throughout and the line of the diaphragm is very irregular. The animal succumbed seven days after the plate was made and showed massive generalized tuberculosis.

per cent of the body weight (0.5 per cent or less being the figure for the normal rabbit (6)). R 5183 remained well and continued to gain weight up to 3,400 g. four and one-half months after the death of the first animal; a final X-ray film of the chest of R 5183 was made and the animal was sacrificed 199 days following inoculation. The X-ray film revealed no pronounced lesions, as shown in figure 3. At autopsy nine small tubercles were found in the lungs, the other viscera showing no lesions.

This study showed that a normally susceptible host (rabbit) may successfully resist inoculation with attenuated organisms, even in large doses. But a comparable host inoculated with virulent organisms *of the same strain* quickly develops lesions demonstrable by X-ray, and succumbs to massive tuberculous infection. It was interesting to note that lesions were readily demonstrable by X-ray fully a month before there was any loss in weight, and that loss of weight occurred only during the final week of life.

Experiments reported previously (6) had demonstrated the marked differences in virulence of the lines of organisms used in the foregoing experiment, both by intravenous inoculation of rabbits and by quantitative titrations of virulence by intracerebral inoculation of carefully matched groups of guinea pigs.

TABLE 3

Differences in mean survival of groups of guinea pigs inoculated intracerebrally with cultures differing in virulence

INOCULATED WITH STRAIN	DOSE	GROUP RECEIVING ATTENUATED CULTURE SURVIVAL	GROUP RECEIVING VIRULENT CULTURE SURVIVAL	PROBABILITY*	NUMBER OF ANIMALS
	mg.	*days*	*days*		
Bovine B-1	0.01	97.25	34.0	655 to 1 (approximate)	4 per group
Bovine B-1	0.000,1	93.25	54.5	215 to 1	4 per group
H37	0.000,01	36.7	27.6	700 to 1	5 per group

* Odds against chance occurrence of difference of similar order. Difference in mean survival was divided by its own probable error. Probability of the resulting figure taken from Pearl ((15) table 40, page 218).

Smaller differences in virulence may be detected by similar methods and are expressed by differences in survival time of inoculated animals, as shown in the following experiment.

Four groups of young, adult, male guinea pigs were selected, each group consisting of four animals. Individual weights and aggregate weights of the groups were similar. Each animal of one group was inoculated intracerebrally with 0.01 mg. of bovine tubercle bacilli, strain B1 (markedly attenuated), and another group with 0.000,1 mg. of the same culture. Each animal of a third group was inoculated intracerebrally with 0.01 mg. of a line of the bovine strain B1, the virulence

of which had been enhanced by animal passage (16); each animal of the fourth group received 0.000,1 mg. of the latter culture.

In addition to the above, two groups, each of five male, albino guinea pigs of matched weight, were inoculated intracerebrally with 0.000,01 mg. of the human strain H37, one group receiving a moderately virulent culture, the second group a culture the virulence of which had been enhanced by animal passage (16). These animals all succumbed to tuberculosis. The mean survival of the six groups, shown in table 3, demonstrates that small or moderate differences in virulence are expressed by differences in survival of the inoculated host. Neither of the bovine B1 cultures was fully virulent, and neither of the human H37 cultures was markedly attenuated, yet significant differences in longevity followed inoculation with the two lines of each. The dose of organisms inoculated into animals included in each horizontal line in table 3 was identical. Thus it is evident that, using the intracerebral route, and inoculating the same dose of different cultures into comparable animals, differences in survival time occur which are proportional to differences in virulence of the cultures.

VARIATIONS IN SURVIVAL TIME DEPENDENT ON THE ROUTE OF INOCULATION

In the concluding study we have investigated the effect of the route of inoculation (portal of entry) on resistance of the host as expressed by survival time. For this analysis animals used as controls in a number of experiments were selected because they had neither been immunized nor treated, because they exhibited no intercurrent illness, because they were of representative stock as regards weight, state of maturity and expected resistance, and finally because each was inoculated with one of two strains of virulent mammalian tubercle bacilli. The analysis includes data from 71 animals inoculated with the human strain H37, and data from 98 animals inoculated with the bovine strain 39 (highly virulent line). In the analysis we have recorded the minimum, maximum and mean survival of groups of animals inoculated with given doses, introduced by various routes. The probable error of the mean survival was determined for each series of animals. These data, together with the number of animals in each series, are recorded in table 4.

Table 4 shows that with either of the two virulent strains there was wide variation in individual survival following subcutaneous inoculation; and with this route of inoculation the mean survival and its probable

error were greatest. With intravenous inoculation (bovine 39) the variation in individual survival was less; the mean survival and its probable error were reduced. But with intracerebral inoculation the variation in individual survival was least, the mean survival was also reduced, and the probable error of the mean survival, even with small numbers of animals, was very low. The three groups of animals inoculated by the three different routes with 0.01 mg. of the bovine strain 39 (table 4) vividly illustrate these points. The data also show that minimal doses of virulent organisms introduced intracerebrally cause death in less time, and with less variation in individual survival time than inocula 10,000 times as great introduced intravenously. The prolongation of survival

TABLE 4

Variations in survival time dependent on the route by which the animals were inoculated

INOCULATED WITH STRAIN	ROUTE OF INOCULATION	NUMBER OF ANIMALS	DOSE	SURVIVAL			
				Minimum	Maximum	Mean	PE_M
			mg.	*days*	*days*	*days*	*days*
Human H37	Subcutaneous	15	0.1	32	213	95.5	9.37
	Subcutaneous	24	0.01	55	322	170.2	12.10
	Intracerebral	32	0.000,01	20	46	28.0	0.63
Bovine 39	Subcutaneous*	4	0.01	100	199	144.2	14.05
	Intravenous*	10	0.01	38	103	58.4	3.96
	Intracerebral	8	0.01	13	21	18.1	0.59
	Intracerebral	8	0.000,1	19	29	22.9	0.78
	Intracerebral	55	0.000,01	14†	63†	32.0	0.78
	Intracerebral	13	0.000,001	23	52	35.5	1.54

* Rabbits. All other animals were guinea pigs.

† Only two died under 21 days and only one lived over 49 days.

with diminishing doses of organisms introduced by the same route is well shown by the four last groups of animals in table 4.

DISCUSSION

Numerous factors which influence the course of infection caused by mycobacteria have recently been discussed by Long (17). He has pointed to the numerous variations in properties of bacteria of the same and of different species and to the variations in susceptibility of individuals of one species, and of different species. Certain of the factors mentioned by Long (17), together with additional ones, have constituted the subjects of the studies here reported. The facts brought out by these ex-

periments point the way to methods of great sensitivity and precision for the bacteriological and immunological investigation of tuberculosis.

Individuals of susceptible stock may effectively resist even intravenous inoculation with large numbers of mycobacteria if those bacteria are low in pathogenic properties (rabbit R 5183, second experiment, as shown in figures 1, 2 and 3). But if the virulence of the organisms is maximal and the host susceptible, death is the result (tables 1, 2 and 4). If the virulent organisms are introduced subcutaneously, resistance of the host has opportunity to express itself, and survival is prolonged. If the virulent organisms are introduced intravenously, lesions are at once set up in visceral organs and resistance of the host is overwhelmed, so that death quickly occurs; and if the inoculation is made intracerebrally, death occurs still more quickly (table 4). With progressive diminution in survival time as influenced by the route of inoculation, there is progressive diminution in variation of survival of different individuals. The resulting decrease in the probable error of the mean survival allows variations in virulence of organisms or in host resistance to be made apparent by relatively small differences in mean survival. The especial significance of these facts is that they maintain even with extremely small inocula introduced intracerebrally. For instance, in the case of the last group of animals in table 4, the mean survival after inoculation of 0.000,001 mg. of organisms was 35.5 $\pm$ 1.54 days. Then if one immunized or treated a comparable group of animals (similar number, of similar age, sex, weight, and from the same breeding stock) and inoculated them with the same dose of the same suspension of organisms, and if the variation in survival was such that the probable error of the mean survival was again $\pm$ 1.54 days, then a difference of seven days in mean survival would be significant.

The result of the titration experiment (table 2) gave useful information on the infectivity of tubercle bacilli. It is agreed by most investigators that 1 mg. of tubercle bacilli freshly removed from the culture represents about 50,000,000 bacteria. If this be the case, then 0.000,000,1 mg. would be five bacteria, and a dose of 0.000,000,01 mg. would be one bacterium for every second animal inoculated. And if one virulent bacterium could induce fatal disease, then just half those receiving 0.000,000,01 mg. should succumb. The results recorded in table 2 closely approximate this hypothetical result and indicate that the minimal infecting dose of tubercle bacilli introduced intracerebrally is very small, approaching a single virulent bacterium.

SUMMARY

A comprehensive study revealed that very striking differences in survival time occurred, depending on whether tubercle bacilli were inoculated subcutaneously, intravenously or intracerebrally. With the intracerebral route of inoculation the survival time was shortest and individual variation in survival time was least.

Employing the intracerebral route of inoculation and groups of guinea pigs selected with care so that their resistance would be as nearly as possible the same, the following conclusive results were obtained. Comparable groups of animals inoculated with the same dose of the same suspension of organisms did not exhibit significant differences in mean survival time. Comparable groups of animals inoculated with different doses of the same suspension of organisms did exhibit significant differences in survival time. And comparable groups of animals inoculated with the same doses of organisms differing in virulence did exhibit significant differences in survival time.

From these results it may be concluded that resistance, as expressed by survival time following inoculation, may be profoundly affected by the virulence of the organisms, the number of them gaining access to the body, and the route by which they enter the body.

REFERENCES

(1) Berg, W. N.: Tubercle, 1935–36, *17*, 496.
(2) Berg, W. N.: Ibid., 1935–36, *17*, 502.
(3) Medlar, E. M., and Sasano, K. T.: Am. Rev. Tuberc., 1933, *28*, 62.
(4) Winn, W. A., and Petroff, S. A.: J. Exper. Med., 1933, *57*, 239.
(5) Steenken, W., Jr., Oatway, W. H., Jr., and Petroff, S. A.: Ibid., 1934, *60*, 515.
(6) Smithburn, K. C.: Am. Rev. Tuberc., 1937, *36*, 637.
(7) Smithburn, K. C.: Ibid., 1937, *36*, 659.
(8) Smithburn, K. C., Sabin, F. R., and Hummel, L. E.: Ibid., 1937, *36*, 673.
(9) Manwaring, W. H.: J. Exper. Med., 1912, *15*, 1.
(10) Feldman, W. H.: Am. Rev. Tuberc., 1930, *21*, 400.
(11) Feldman, W. H.: Ibid., 1934, *29*, 415.
(12) Boquet, A., and Broca, R.: Ann. Inst. Pasteur, 1935, *55*, 8.
(13) Smithburn, K. C.: J. Exper. Med., 1936, *64*, 771.
(14) Corper, H. J., and Cohn, M. L.: Am. J. Hyg., 1933, *18*, 1.
(15) Pearl, R.: Medical biometry and statistics, Philadelphia, W. B. Saunders and Co., 1923.
(16) Smithburn, K. C.: Am. Rev. Tuberc., 1939, *39*, 116.
(17) Long, E. R.: Science, 1938, *87*, 23.

RESISTANCE TO TUBERCULOSIS[1]

II. Variations Dependent on the Age of the Host and upon Resistance Induced by Vaccination

KENNETH C. SMITHBURN

Numerous host-related factors are now known which have an influence on, or in part determine the resistance to tuberculosis. The classic work of Theobald Smith demonstrated variations in resistance dependent on the species. He (1) showed that, while guinea pigs and rabbits are both susceptible to infection with bovine tubercle bacilli, of these two o ly the guinea pig is susceptible to infection with human type organisms. These observations on the variations in native resistance have been extended to include many animal species and various types of mycobacteria.

Through the work of Wright and Lewis (2), Lurie (3), and Opie and Freund (4), and others, it is now evident that within a given animal species there are genetically transmissible differences in resistance to a given type of tubercle bacillus. Moreover, there is clinical evidence that within one individual there are periodic variations in resistance to tuberculosis, the periods of lowest resistance being puberty, the child-bearing period in women, and the age of the pseudoclimacteric in men.

Regarding the relative resistance of children and of adults, opinions are at variance. Some clinicians hold that resistance is low in childhood and increases with age without regard to altered resistance induced by manifest or latent infection. Others maintain that infants and children are natively more resistant than adults, and that resistance declines with age. An increasing number of workers, led by the Lymanhurst group (5, 6), believe that resistance to primary infection is high at any age, but that resistance to reinfection is much less effective.

The comprehensive experimental studies on antituberculosis vaccination have conclusively demonstrated that resistance can be increased by such procedures, although not without concomitant acquisition of tuberculin hypersensitiveness, the rôle of which in immunity is uncer-

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tain. The phenomenon of Koch (7) was probably the first evidence of altered tissue reaction depending on prior experience of the host with the organisms. The various workers who have employed heat-killed organisms, including Römer (8), Petroff (9), Opie and Freund (4) and many others, and the large group who have studied vaccination with BCG have shown beyond doubt that resistance of normal individuals may be at least temporarily increased by active immunization.

In the studies to be reported we have investigated the relative resistance of young and older animals to tuberculosis and have carried out certain experiments on prophylactic vaccination, namely, tests of the efficacy of heat-killed virulent organisms, heat-killed attenuated organisms and living attenuated organisms.

MATERIALS AND METHODS

Animals: Albino guinea pigs, bred at this Institute and from stock free of epizootic streptococcal infection, were used in the first two experiments. In the third experiment the animals used were from commercial stock, all of them free of streptococcal infection as determined by the intracutaneous test of Moen (10). The age, weight and sex of the animals will be discussed under individual experiments. Males and females were separately caged; not more than 4 animals were caged together. All were isolated and observed for evidence of infection prior to any experimental procedure. Only vigorous, healthy animals were used.

Cultures, suspensions and inoculations: The bacteria used for the test inoculations were a highly virulent line of the human strain H37, a moderately virulent line of the same strain, and a highly virulent line of the bovine strain 39 isolated by the late Dr. Theobald Smith (11). These were grown on Corper's glycerolated egg-yolk medium (12) adjusted to pH 6.8. Vigorously growing cultures about three weeks old were used.

Suspensions were prepared by grinding a weighed quantity of organisms, freshly removed from the culture, in a sterile porcelain mortar with drop-wise addition of saline so that 1 cc. of suspension contained 1 mg. of bacteria. From this, appropriate dilutions were prepared to contain the amount of organisms desired for inoculation. All inoculations were done intracerebrally by the method previously described (13), the desired dose of organisms being injected in 0.1 cc. of saline. Anaesthesia for intracerebral inoculations was induced either with ether

or by intraperitoneal injection of 0.5 per cent saline solution of seconal,[2] the dose of the latter being 20 mg. per kilogram.

Vaccines: The bacteria used for preparing vaccine were two lines of the bovine strain 39. One, highly virulent, was grown on Corper's medium adjusted to pH 6.8. The second line had lost virulence while under serial subcultivation on Corper's medium adjusted to pH 6.0 (14, 15). Suspensions of these two lines of organisms were prepared in saline so that 1 cc. contained 1 mg. of bacteria. The suspension of attenuated organisms was divided into two portions, one of which was diluted tenfold and reserved for use as living vaccine. The second portion and the suspension of virulent organisms were immersed in a water bath and heated at 60°C. for one hour, care being taken that no organisms escaped full exposure to the heat.

The procedure of the vaccinations will be described in the discussion of the third experiment.

Measurement of results: Variations in resistance were determined by differences in the mean survival time of groups of animals. The significance of the differences was determined by mathematical analysis. The probable error of the mean survival was determined.[3] The difference in mean survival of groups to be compared was determined and the probable error of this difference was calculated. The result was considered significant only when the difference in mean survival was three or more times its own probable error. The probability of such differences was ascertained from Pearl's (16) table 40 (page 218).

At death an autopsy was performed on each animal and surveys were made to determine the extent of macroscopical lesions. Paraffin sections were prepared of brain, lung, spleen, liver, tracheal and cervical lymph nodes of each animal, and stained by Goldner's modification of the Masson trichrome stain (17). In addition, sections of brain, spleen and lung of each animal were stained for tubercle bacilli by the method described by Fuller (18). From the sections microscopical surveys were made to ascertain quantitative and qualitative differences in the lesions of the animals.

[2] Sodium-Propyl-methyl-carbinyl Allyl Barbiturate, Lilly, generously supplied by Eli Lilly and Company, through the courtesy of Dr. G. F. Kempf, Indianapolis City Hospital.

[3] For all data included in this report the formula for small samples $\left(\sigma = \frac{\sqrt{\Sigma (V-M)2}}{N-1}\right)$ was used in determining the standard deviation.

VARIATIONS IN SURVIVAL TIME DEPENDENT ON THE AGE OF THE HOST

Although differences in the reaction of young and of older animals to tuberculin have been demonstrated by Freund (19), differences in resistance to tuberculosis dependent on age have not, to our knowledge, been demonstrated. It is well known that young and older animals react dissimilarly to other infectious agents (20). Therefore the following two experiments were designed to ascertain the relative resistance of immature and mature animals to tuberculosis.

First experiment: The animals used for this experiment were of albino stock bred in this Institute. There were 3 females weighing from 840 g. to 1,060 g. and 4 immature males weighing between 120 g. and 180 g. Each of the 7 was inoculated intracerebrally under seconal anaesthesia with 0.001 mg. of the highly virulent bovine strain 39. Seven other animals, including 2 males and one female weighing between 680 g. and 860 g., 2 males and 2 females weighing between 100 g. and 140 g., were inoculated intracerebrally under seconal anaesthesia with 0.001 mg. of the moderately virulent line of the human strain H37. All were allowed to succumb to the disease without other experimental procedure.

Results: Of the 14 animals included in this experiment, 2 died from extraneous cause (nontuberculous pneumonia) and were excluded from further consideration. The average survival of the old animals inoculated with the bovine strain 39 was 21.5 days, as compared with 27.25 days for the young. The average survival of the old animals inoculated with the human strain H37 was 31.3 days; the average for the infant animals was 32.6 days. These differences were suggestive but not conclusive.

This was a preliminary experiment and it was considered probable that the uncertainty of the result was due to the large dose of organisms inoculated. The results, especially in the animals inoculated with the bovine strain 39, seemed suggestive, so that it was decided to conduct a similar, larger experiment using a smaller dose of bacteria.

Second experiment: Three groups of albino guinea pigs were inoculated in this experiment. One group included 3 females and 2 males weighing between 860 g. and 1,040 g., each approximately eighteen months old. A second group included 5 males weighing between 380 g. and 480 g., each approximately three months old. The third group included 5 females weighing from 100 g. to 160 g., each about two weeks old. Each of these 15 animals was inoculated intracerebrally

under seconal anaesthesia within the same hour with the same dose of the same suspension of organisms, namely, 0.000,01 mg. of the highly virulent line of human tubercle bacilli, strain H37. All were allowed to succumb to the disease without other experimental procedure.

Results: The mean survival of the three groups of animals is shown in table 1, together with the range of survival and the probable error of the mean survival.

From table 1 it will be seen that the survival time following inoculation was inversely proportional to the age of the animals. The old succumbed first, the middle age group succumbed next, and the younger animals succumbed last. When all three groups were considered there was overlapping of deaths among the groups. But, disregarding for the moment the animals of the middle age group, all animals of the older

TABLE 1

Variations in survival after intracerebral inoculation of 0.000,01 mg. human tubercle bacilli—animals of different age and weight

GROUP	NUMBER OF ANIMALS	MEAN WEIGHT	SURVIVAL			
			Minimum	Maximum	Mean	PE_M
		grams	*days*	*days*	*days*	*days*
A	5	988	19	27	23.8	0.89
B	5	424	22	33	27.6	1.22
C	5	128	32	39	35.8	0.87

Difference B − A, 3.8 days is 2.5 × its PE. Odds 9.9 to 1.
Difference C − B, 8.2 days is 5.5 × its PE. Odds very high.
Difference C − A, 12.0 days is 9.6 × its PE. Odds very high.

group succumbed before the time of the first death among the infant animals. Differences in survival time, of the order observed here (table 1) have been shown (21) not to occur when animals of similar age and weight are inoculated with the same dose of the same suspension of organisms. But the differences recorded in table 1 are even more striking when it is noted that the dose of organisms for the young animals, expressed as mg. of bacteria per kilogram body weight, was 7.7 times the dose given to the old and 3.3 times the dose given to the group of middle age. It is therefore apparent that resistance to a given inoculum varies with age and is inversely proportional to it.

Microscopical studies of the lesions which developed in these three groups of animals showed no essential differences in the type of lesions, nor in their distribution. All animals exhibited acute tuberculous

meningoencephalitis and metastatic visceral tuberculosis. But both the local and metastatic visceral lesions were the more extensive in the young animals, and least extensive in the oldest animals. From the histological studies it appeared that the infection proceeded in similar fashion and at a similar rate in young and older animals, but that less tuberculosis was necessary to cause death in the older animals. Lesions were the more extensive in the youngest animals because they lived longest.

STUDIES ON RESISTANCE INDUCED BY VACCINATION

Several experiments on antituberculosis vaccination have been carried out in this laboratory, employing methods similar to those in the experiment which follows. The results of all were in agreement.

The purpose of the experiment was to compare the protective properties of living attenuated, and killed virulent organisms, and to ascertain if the immunizing principle of attenuated organisms is thermolabile.

Third experiment: Vaccines consisting of suspensions of (*a*) living attenuated organisms, (*b*) heat-killed attenuated organisms, and (*c*) heat-killed virulent organisms, were prepared as described under Materials and Methods. The suspension of living organisms contained 0.1 mg. of bacteria per 1 cc. The suspension of heat-killed organisms contained 1.0 mg. per 1 cc. The vaccines were injected daily by the subcutaneous route on the right side. The daily dose was 0.2 cc. and five doses were given, so that those injected with living attenuated organisms received a total quantity of 0.1 mg. of organisms, and the two series injected with heat-killed bacteria received a total quantity of 1.0 mg. per animal.

Fifty-six male guinea pigs obtained from commercial stock were isolated and observed for a week. During this time each was tested intracutaneously for streptococcal infection by the method of Moen (10) with extract generously supplied by him. Three animals were found to be reactors and were discarded. Each of the 53 remaining animals weighed between 360 g. and 420 g. at the start of the experiment. The animals were first subdivided into four groups. One group of 13 served as controls and were not vaccinated; a group of 11 were vaccinated with heat-killed virulent organisms; a group of 11 were vaccinated with heat-killed attenuated organisms; and a group of 18 with living attenuated organisms. Of the latter series (vaccinated with living attenuated organisms) 4 individuals were reserved without further experimentation to ascertain whether the living vaccine produced progressive disease.

Following the vaccinations the animals of each series gained weight, with a single exception.[4] The gain in weight was approximately the same in the four series of animals and bore no relation to experimental procedures.

Forty-four days following the last vaccinations the four series of animals were subdivided as shown in table 2. Approximately one-third of each series was included in each subgroup. Each animal of one subgroup of controls and each animal of one subgroup of the three series previously vaccinated were then inoculated intracerebrally with 0.01 mg. of highly virulent bovine tubercle bacilli, strain 39. One subgroup of the controls and one subgroup of each vaccinated series were similarly inoculated with 0.000,1 mg. of the same strain of organisms. The remaining one-third of the animals, including one subgroup of the non-vaccinated controls and one subgroup of each vaccinated series, were inoculated intracerebrally with 0.000,001 mg. of the same strain of bacilli. These inoculations were done under ether anaesthesia. Eight of the subgroups included 4 animals each, two included 3 animals each, one included 5 animals and one included 6 animals, as shown in table 2. Following the test inoculations the animals were allowed to succumb without other experimental procedure.

At death a necropsy was done on each animal, and gross surveys of the lesions were made. Microscopical sections of the tissues were made as described under Materials and Methods, and the four series of animals were compared as regards type, distribution and extent of lesions.

Results: The 4 animals which were vaccinated with the living attenuated organisms, but not inoculated with virulent organisms, remained well and gained weight. One hundred and ninety-five days following the last dose of vaccine each was sacrificed to ascertain whether the living bacteria used as vaccine had induced disease. Only one of the 4 exhibited lesions at necropsy; these consisted of a few small hard nodules in the spleen. Microscopically these lesions were fibrotic tubercles. In one of them a single acid-fast bacillus was found. This animal showed no other microscopical lesions, and the remaining 3 animals showed no lesions whatever. This result indicated that the organisms were indeed attenuated, as we had previously observed (15).

[4] This animal, one of those vaccinated with killed virulent organisms, and subsequently inoculated with the largest test dose, did not gain weight at any time. However, it did survive the test inoculation for a period slightly longer than the mean for the group, and the pathological findings were in no wise different from those of experimental mates.

Table 2 shows the result of the experiment on prophylactic vaccination. The survival time of each animal following test inoculation and the mean survival time of each group is recorded.

The very slight differences in mean survival time of two of the vaccinated groups and the control group inoculated with 0.01 mg. of organisms were not significant. The differences between the mean survival time of controls and of each vaccinated group receiving 0.000,1

TABLE 2

Survival time of each individual and mean for each group, in three series of vaccinated animals and in their nonvaccinated controls

TEST INOCULATION DOSE	CONTROLS NONVACCINATED		VACCINATED WITH HEAT-KILLED VIRULENT TUBERCLE BACILLI		VACCINATED WITH HEAT-KILLED ATTENUATED TUBERCLE BACILLI		VACCINATED WITH LIVING ATTENUATED TUBERCLE BACILLI	
	Survival time in days following inoculation							
	Individual	Mean	Individual	Mean	Individual	Mean	Individual	Mean
mg.								
0.01	18	19.0	19	21.6	15	20.3	Died overnight	
	18		20		21			
	20		26		25			
	20							
0.000,1	19	20.25	30	34.0	31	39.5	28	38.0
	20		33		34		37	
	21		35		46		37	
	21		38		47		57	
0.000,001	29	38.8	35	79.5	37	45.0	37	72
	33		43		37		39	
	35		57		41		45	
	45		183*		65		47	
	52						119	
							145	

* This animal was sacrificed when in good health to terminate the experiment. No macroscopical lesion was found. In sections a single minute "hard" tubercle was found in the cerebellum. No tubercle bacilli were found in the lesion.

mg. were significant by direct analysis; and in the groups receiving 0.000,001 mg. of organisms the differences proved also to be significant.[5] Moreover, the one vaccinated animal (table 2) which was sacrificed to terminate the experiment, survived the test inoculation.

[5] In the latter instance the variability was so great, and consequently the probable error of the mean survival was so great, that direct analysis did not reveal the significance of the result. However, this was brought out by arranging each vaccinated group with the control

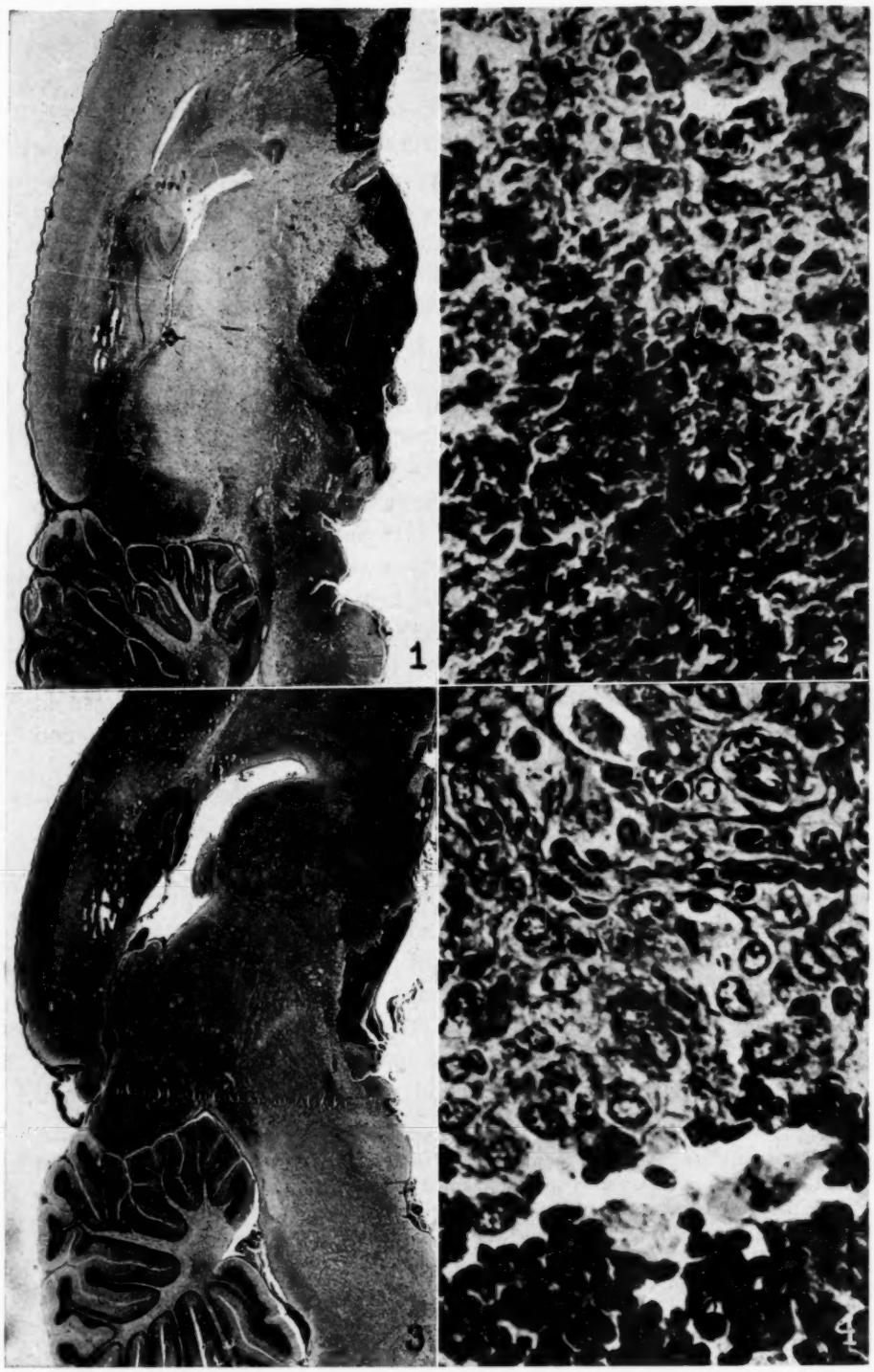
Thus, while only one animal survived as result of the vaccinations, survival time was prolonged in all the vaccinated groups receiving either 0.000,1 mg. or 0.000,001 mg. But there was no demonstrable protection in the groups inoculated with 0.01 mg. Indeed the group vaccinated with living attenuated organisms and inoculated with 0.01 mg. succumbed during the night following inoculation (table 2). Similar results were observed by Soper and Dworski (23) and it is clear that the allergy induced by vaccination may have a detrimental effect if the superinfecting dose is large.[6]

The histological studies of animals included in this experiment revealed additional evidence of a protective effect. All of the control animals, even those receiving the 0.000,001 mg. dose of virulent organisms, exhibited generalized tuberculous meningoencephalitis, as shown in figures 1 and 2. Figure 1 is a photograph at low magnification of the brain of the control animal, R 5170, inoculated with 0.000,001 mg. Death occurred on the forty-fifth day. Like its experimental mates this animal showed extensive meningitis, and lesions in remote viscera (spleen, liver, etc.). Figure 2 from the same animal shows, at higher magnification, the character of the lesions shown in figure 1. The exudate is composed of epithelioid cells, neutrophiles and monocytes, and there is a good deal of caseation.

In contrast to these findings many of the vaccinated animals, especially those which lived the longer, exhibited no meningitis, or at least only localized inflammation. Instead, there was present in the brain, and usually at the base on the side of inoculation, a localized tubercle of greater or lesser size. Such a lesion is shown at low magnification in figure 3 and at higher magnification in figure 4. There is no caseation. At the lower margin of the lesion there is a closely packed mass of lymphocytes. The lesion itself is composed almost wholly of epithelioid cells. These photographs were made of the brain of guinea pig R 5161, of the group vaccinated with heat-killed virulent organisms and

as one series, and determining the standard deviation. Then, employing the method shown by Davenport and Ekas ((22) page 21) the significance of the result was shown by the fact that one animal in each vaccinated group could be rejected as an extreme variate. Thus, while the controls were a normal series, each of the vaccinated groups receiving 0.000,001 mg. contained individuals showing extreme variation in survival time, and this extreme variation was undoubtedly a result of partial protection afforded by the vaccination.

[6] This effect is not characteristic alone of intracerebral inoculation. In other studies we have vaccinated rabbits to produce immune serum for serological work. Animals previously vaccinated, then allowed to rest, and again injected with as little as 0.3 mg. of killed bacilli, frequently succumbed during the next twelve to twenty-four hours.



FIGS. 1–4

inoculated with 0.000,001 mg. of bovine strain 39. Death in this animal occurred forty-three days following inoculation. By comparing figure 3 with figure 1 it may be seen that the lesions of the vaccinated animal (figure 3) were quite localized. And figure 4 shows that the local lesion differed histologically from that in the control, figure 2. A further difference between such vaccinated animals and their controls was that the vaccinated guinea pigs exhibited little or no visceral tuberculosis, while the controls invariably showed lesions in spleen, liver and lymph nodes. Thus, in animals which developed appreciable immunity or resistance as a result of vaccination there was concomitantly developed a power to localize the virulent organisms and to prevent their spread to remote parts of the body. The immune reaction, however, was not adequate to destroy the bacilli *in situ*, and there they remained, perhaps multiplying slowly and eventually causing death either from paralysis and inanition or by involvement of some vital cerebral centre.

DISCUSSION

The fact that resistance to tuberculosis varies with age, and that this variation is characterized by a progressive decline in resistance with advancing age, must be taken into account in any experiments in which the attempt is made to influence the course of the disease either by treatment or by prophylactic measures. Especially is this true when the criterion of effect is the survival time following inoculation. In large groups of animals inoculated by the intracerebral route, very small

FIG. 1. Saggital section of left cerebral hemisphere of guinea pig R 5170, a nonvaccinated control inoculated intracerebrally with 0.000,001 mg. of the bovine strain 39. Animal succumbed on the forty-fifth day following inoculation. Note very extensive meningitis and involvement of brain substance at the base, and lesions in cerebellum. Masson trichrome stain. 5.5 ×

FIG. 2. Representative area from same section as fig. 1, showing character of the meningeal reaction. Lower portion of photograph shows border of a caseous focus. Elsewhere the cellular reaction is complex and shows many neutrophiles. There is much cellular degeneration. Masson trichrome stain. 720 ×

FIG. 3. Saggital section of left cerebral hemisphere of guinea pig R 5161, which was vaccinated with heat-killed virulent organisms and inoculated intracerebrally with 0.000,001 mg. of the bovine strain 39. Death occurred on the forty-third day following inoculation. Note circumscribed lesion at base of brain, minimal meningitis and absence of cerebellar lesions. Masson trichrome stain. 5.5 ×

FIG. 4. Higher magnification of the lesion seen at the base of the brain in fig. 3. Note absence of caseation. The lower border of the lesion is heavily infiltrated with lymphocytes. The tubercle is made up almost wholly of epithelioid cells which show no degenerative change. Masson trichrome stain. 720 ×

differences in mean survival time may be highly significant, as we have shown (21). Then if age differences be not taken into account, an apparent beneficial effect might prove to be a false one; or a truly beneficial effect might be masked by differences in resistance due to age. These facts emphasize the great importance of careful selection of experimental hosts, with especial regard to the age and weight.

The greater resistance of the young individual to tuberculosis which we have observed experimentally is in accord with the experience of certain clinicians. Although the young guinea pig lacks the power which many believe to be indigenous in children—the power to heal a primary infection—and may therefore be considered less resistant than a young human being, resistance of the older guinea pig is still less, and significantly so.

As regards resistance induced by vaccination, our experiments confirm those of Soper and Dworski (23) that enhanced resistance may be so induced, but our results do not indicate the better protection with living attenuated organisms. Instead, we are led to believe, as do Opie and Freund (4) and as did Petroff (9), that the result to be obtained with killed virulent organisms is equally good. However, the hypersensitiveness induced by vaccination cannot be ignored, and we observed, as did Soper and Dworski (23), that a large infecting dose may cause early death in a sensitized individual.

It may well be that our results and those of Soper and Dworski (23) offer a clue to the old controversy as to the relation of allergy and immunity. It is generally agreed by all participating in this controversy that the immunized resistant host is allergic; to certain workers this has indicated a direct relationship; but others have maintained that immunity is a thing apart from allergy. Certainly it is true that an allergic host may not be unusually resistant (24). If, then, a certain quantity of allergen is necessary to evoke the allergic response, the sensitized animal which received a small test inoculation might demonstrate the immune response without exhibiting allergic reaction. But if the inoculating dose were sufficient to contain the necessary quantity of allergen, then the allergic reaction might, by explosive violence, quickly kill the host. In such case the allergic state would be detrimental only when the superinfecting dose was larger, but in any case might bear no closer relation to immunity than does allergy in a host which is not immune (24).

However this may be, in clinical practice the dose of organisms with

which man becomes infected cannot be controlled as in the laboratory; and it follows that occasional untoward results might be expected in any large program of antituberculosis vaccination. Moreover, as we have recently shown (25) attenuated organisms may regain virulence through host to host passage. Therefore, in our opinion, vaccination by any method now known is not without its dangers; and the potential dangers are greater in the case of vaccine composed of living mycobacteria.

There is a possibility that the immunizing substance, or substances, contained in the organisms may be separate and distinct from those which induce allergy. Should this be the case, isolation of the immunizing antigen would eliminate the difficulties just discussed.

The capacity of the resistant vaccinated animal to localize bacteria inoculated intracerebrally, together with the absence of meningitis and of visceral lesions, leads to another interesting speculation. Lesions similar in kind have been observed (25) in animals surviving long after intracerebral inoculation with attenuated organisms. This gives rise to the question whether the virulent organisms injected into immunized animals might not have suffered a decline in virulence while residing in the resistant host. Such a change could be detected experimentally but opportunity to investigate this point has not been available.

The results recorded in table 2 do not indicate that the immunizing antigen in tubercle bacilli is thermolabile.

SUMMARY

Variations in resistance to tuberculosis depending on the age of the host have been studied by sensitive methods. Young individuals proved to be the more resistant, and there is a progressive decline in resistance with advancing age.

Resistance induced by vaccination was expressed by greater survival time of vaccinated individuals following intracerebral inoculation of small doses of virulent organisms. The resistant host has a capacity to localize the organisms and restrict them to the brain, but there the organisms survive. An occasional vaccinated animal may survive the virulent inoculation.

Hypersensitiveness accompanying the enhanced resistance may cause death if the infecting dose is large.

Certain implications of the work are discussed.

REFERENCES

(1) SMITH, T.: J. Exper. Med., 1898, *3*, 451.
(2) WRIGHT, S., AND LEWIS, P. A.: Am. Naturalist, 1921, *55*, 20.
(3) LURIE, M. B.: In Tuberculosis and leprosy, the mycobacterial diseases, F. R. Moulton, Editor, The American Association for the Advancement of Science, 1938, p. 25.
(4) OPIE, E. L., AND FREUND, J.: J. Exper. Med., 1937, *66*, 761.
(5) MYERS, J. A.: Am. Rev. Tuberc., 1933, *27*, 121.
(6) STEWART, C. A.: Am. J. M. Sc., 1933, *185*, 346.
(7) KOCH, R.: Deutsche med. Wchnschr., 1891, *17*, 101.
(8) RÖMER, P. H.: Beitr. z. Klin. d. Tuberk., 1909, *13*, 1.
(9) PETROFF, S. A.: J. A. M. A., 1927, *89*, 285.
(10) MOEN, J. K.: J. Exper. Med., 1936, *64*, 553.
(11) SMITHBURN, K. C.: Ibid., 1935, *62*, 645.
(12) CORPER, H. J., AND COHN, M. L.: Am. J. Hyg., 1933, *18*, 1.
(13) SMITHBURN, K. C.: J. Exper. Med., 1936, *64*, 771.
(14) SMITHBURN, K. C.: Ibid., 1936, *63*, 95.
(15) SMITHBURN, K. C.: Am. Rev. Tuberc., 1937, *36*, 637.
(16) PEARL, R.: Medical biometry and statistics, Philadelphia, W. B. Saunders Co., 1923.
(17) GOLDNER, J.: Am. J. Path., 1938, *14*, 237.
(18) FULLER, D. S.: J. Lab. & Clin. Med., 1938, *23*, 416.
(19) FREUND, J.: J. Immunol., 1927, *13*, 285.
(20) SABIN, A. B., AND OLITSKY, P. K.: J. Exper. Med., 1937, *66*, 15, 35.
(21) SMITHBURN, K. C.: Am. Rev. Tuberc., 1939, *39*, 371.
(22) DAVENPORT, C. B., AND EKAS, M. P.: Statistical methods in biology, medicine and psychology, New York, John Wiley and Sons, Inc., ed. 4, 1936.
(23) SOPER, W. B., AND DWORSKI, M.: Am. Rev. Tuberc., 1925, *11*, 200.
(24) SMITHBURN, K. C., SABIN, F. R., AND GEIGER, J. T.: Ibid., 1934, *29*, 562.
(25) SMITHBURN, K. C.: Ibid., 1939, *39*, 116.

THE DEMONSTRATION OF TUBERCLE BACILLI BY CULTURE AND BY GUINEA PIG INOCULATION[1]

A Comparative Study

ALBERT GUGGENHEIM AND MAX FINKELSTEIN

Both as a diagnostic procedure and as an indicator of therapeutic results in many forms of tuberculosis, the demonstration of tubercle bacilli in various materials is of the utmost clinical importance. The diagnosis of tuberculosis often can be regarded as certain only after the organism has been found, whether it be in the sputum, urine, pleural fluid or the discharge of a sinus. Once the diagnosis has been made, the absence of the organism from material, in which it could previously be demonstrated, constitutes perhaps the most important single factor in evaluating the result of treatment.

It is with good reason, therefore, that methods for the demonstration of tubercle bacilli in all sorts of material have engaged the attention of many workers.

Because of its simplicity, cheapness and speed, the direct smear of suspected material, stained to demonstrate acid-fast organisms, is the most common procedure in use for this purpose. In a large proportion of cases this method suffices to demonstrate the organism. It has been conclusively shown, however, that considerable numbers of tubercle bacilli may be present in a specimen in which acid-fast organisms cannot be found by this technique. Corper (1) states that before tubercle bacilli can be discovered with regularity in direct smears of sputum, they must be present in numbers greater than 100,000 in each cubic centimetre. By repeated examinations, and by employing one or more of the various concentration methods, organisms can undoubtedly be found in specimens that would otherwise be classed as negative. But there remains a large gap between the specimen negative by direct smear and that in which no organisms can be demonstrated by any method. The relative sensitivity of direct smear, of culture and of guinea pig inoculation may be judged from the report of Saenz and Costil (25), who state that positive

[1] From the Medical Department of the National Jewish Hospital, Dr. Charles J. Kaufman, Medical Director, Denver, Colorado.

cultures can be obtained from material containing forty bacilli, and positive guinea pigs when the specimen contains as few as twenty bacilli. Nevertheless, in a few cases, culture and guinea pig may be negative when the direct smear is positive. Corper and Uyei (2) cultured ninety-three microscopically positive sputums and obtained positive results in 91.4 per cent. In our own series, one specimen of pleural fluid, positive on direct smear and by means of guinea pig inoculation, was negative by culture. Similar reports by other authors can be found in the literature.

LITERATURE

The relative merits of culture, on the one hand, and guinea pig inoculation on the other, is a subject still under dispute. In reviewing the literature, we have restricted ourselves to those studies based on parallel examination of identical material by culture and by guinea pig inoculation. Only in this way can one eliminate the factor of unequal bacillary content in the material subjected to one method of examination or the other.

Corper (1) using his own crystal-violet-potato medium, and 6 per cent sulphuric acid to destroy contaminating organisms, found as high a percentage of positive results by culture as by guinea pig inoculation. In a later publication Corper and Uyei (2) confirmed these findings. Norton, Thomas and Broom (5), using modifications of Petroff's and of Petragnani's media, found culture superior to guinea pig inoculation. In a series of 151 specimens (pleural fluid, urine, spinal fluid and others) negative on direct smear, culture was positive in 51 cases, guinea pig in 38 cases. These investigators found that not all specimens positive by direct smear were positive by culture.

McNabb and Wilson (6) found culture methods superior to guinea pig inoculation in the examination of sputum. In 66 out of 85 positive specimens the guinea pig was positive; whereas culture was positive in 75 cases. Woolley's and Petragnani's media were used by these investigators. Mishulov, Romano, Melman and Kereszturi (7), using the Bordet-Gengou and Loewenstein media, found a higher proportion of positives by culture methods than by guinea pig inoculation.

Frankl (8) obtained positive results as often by culture on Hohn's medium as by guinea pig inoculation, and recommends that both methods be employed. Similar advice is given by Paponnet (13) who found that culture by Loewenstein's method was superior to guinea pig inoculation. Limito (9) employing Petragnani's medium, Ruys (10) and

Schnittler (11) both using Loewenstein's medium, and DeGironcoli and Bortolozzi (12) state that cultural and biological methods each give about the same percentage of positive results.

The majority of investigators emphasize the superiority of guinea pig inoculation over culture methods. Stadnichensko and Sweany (14) report that among 69 specimens of sputum found positive by combined culture and guinea pig inoculation, 33 were positive by the latter means alone, and only 3 positive by culture alone. According to these authors, guinea pig inoculation is superior to culture when contaminated material is to be examined. Magath and Feldman (26) found that guinea pig inoculation gave a higher percentage of positives than culture, if the material under examination was negative on direct smear. They regard guinea pig inoculation as superior also because virulence can be proved by this means alone. On several occasions they obtained acid-fast organisms by means of culture in cases later proved nontuberculous pathologically. Guinea pigs injected with the same material were negative. Three culture methods were used by these investigators—that of Corper and Uyei, of Sweany and Evanoff and of Miraglia. Farjot's (15) results indicated that the guinea pig enjoyed a slight superiority over culture. Blair and Hallman (16), using Corper and Uyei's potato medium and guinea pig inoculation in examining 44 specimens obtained from cases of nonpulmonary tuberculosis, reported that in 5 cases the guinea pig was positive when the culture was negative. Ronzini (17) compared culture by various methods (Petroff, Lubenau, Petragnani) with guinea pig inoculation, and concluded that the latter was the most reliable method for demonstrating tubercle bacilli (92.9 per cent of all positive results). The best results by culture methods (80.4 per cent of all positives) were obtained on Petragnani's medium. Graziosi (18) found guinea pig inoculation superior to both Petragnani's and to Corper and Uyei's media. Blanco (19) could demonstrate tubercle bacilli in 16.6 per cent of 129 specimens by means of Hohn's and Mouriz's media; by means of guinea pig inoculation, 22.2 per cent were positive. Among 133 positive specimens, Holst (20), using Hohn's medium, found 50 positive by both culture and guinea pig inoculation. Guinea pig alone accounted for 79 positive specimens, culture alone for 4 positives. Levin (21) found 310 positive specimens among 800 gastric contents obtained from children. Of these, 93 per cent were positive by guinea pig inoculation, 31 per cent by culture. However, culture was positive in 19 instances where guinea pig inoculation gave a negative result. Daddi

(22) examined 365 microscopically negative specimens. He found 77 positive both by culture and guinea pig inoculation; 30 by guinea pig inoculation only; 22 positive by culture only. Petragnani's medium was used by this author. Gelberg and his coworkers (23) and Natin (24) report similar results with Petragnani's and with Loewenstein's medium.

PROCEDURE

During the period from 1928 to 1938, 504 specimens of clinical material derived from 389 patients were examined for tubercle bacilli by parallel culture and guinea pig inoculation. Each individual specimen was examined by both methods. This permits comparison between the methods themselves, without the complicating factor of differences between the specimens used for one method of examination or the other. The specimens comprised the following:

Sputa	256
Gastric contents	38
Urines	116
Pleural fluids	47
Pus	26
Miscellaneous	21

The miscellaneous group consisted of 3 ascitic fluids, 11 spinal fluids, 3 stools, 3 specimens of biopsy material and one pericardial fluid.

During the period of the study, the laboratory personnel changed a number of times, and a number of changes were made in the technique of culture and of animal inoculation. From 1928 to 1934, all material was cultured on the crystal-violet-potato medium of Corper and Uyei (2); from 1928 to 1930, 2 per cent sodium hydroxide was used to digest the material and destroy contaminants; from 1931 to 1934, 6 per cent sulphuric acid was used in place of the sodium hydroxide (2). From 1935 to the present, 5 per cent oxalic acid (3) was used to destroy contaminants, and both Corper's potato medium and Corper and Cohn's egg medium (4) were used in culture. The number of tubes planted varied from three to eight; when three tubes were used, one tube of potato medium and two of egg medium were used as a rule.

A culture was considered positive when, within a period of three months or less, growth became visible to the naked eye, and acid-fast organisms could be demonstrated in smears of the colonies. If one tube out of the entire number planted was positive, the specimen was reported as positive. In those cases where all tubes became contaminated, the specimen was discarded for purposes of this study.

Only one guinea pig was injected with each specimen. Examinations in which animals were injected several times were discarded for the purposes of this study. Until 1935, the animals were injected intracutaneously or subcutaneously. From 1935 to the present, each animal was injected intraperitoneally and intracutaneously, using portions of the same specimen, at the same time. A guinea pig was considered positive if, on autopsy, gross lesions characteristic of tuberculosis in that animal were found, and acid-fast organisms were found in smears from these lesions or in histological sections. Unless an animal died, it was not autopsied until at least ninety days after inoculation. If a guinea pig died prematurely, so that no time was afforded for the development of tuberculous lesions, the examination record was not used for the purposes of this study.

In 118 instances, the identical specimen used for culture and guinea pig inoculation was negative for tubercle bacilli on direct smear. In most of the remaining cases, no smear was done on the specimen involved; but the majority of specimens were derived from cases that had previously provided similar specimens in which no bacilli could be demonstrated by direct smear. This was true particularly of sputum, no specimen of which was submitted for culture and animal inoculation unless previous specimens had been negative repeatedly by direct smear and concentration methods. In the period from 1935 to 1938 the number of direct smears examined was greatly increased, a fact that is reflected in the results of both cultures and guinea pig inoculations during this time.

RESULTS

The results of this investigation are summarized in tables 1 to 5.

Table 1 gives the percentage of positive and negative results by combination of culture and guinea pig inoculation, for the entire material studied, and for each type of material. Of the entire material, 36.7 per cent was positive for tubercle bacilli. The highest percentage of positives was found in pus, 61.5 per cent; pleural fluid was next, with 59.6 per cent; then sputum with 38.3 per cent; the miscellaneous group with 38 per cent; urine with 25.9 per cent; and finally gastric contents with 13.2 per cent positive. The low percentage of positives among gastric contents can be explained on the basis of the derivation of the specimens. They were obtained from cases having no expectoration, or having sputum that had been found negative one or more times by direct smear and culture; at times from nontuberculous cases, for diagnostic

purposes. Some specimens were obtained from cases of extrapulmonary tuberculosis, without pulmonary involvement. A few gastric contents were obtained from cases of active or healed primary tuberculosis in children. The relatively high proportion of positives among specimens of pus and pleural fluid, compared to sputum, can be explained by the more frequent examination of the latter by means of direct smear before the material was cultured and injected into guinea pigs. As a rule, sputum was examined repeatedly by direct smear or concentration methods, and only if found persistently negative was a specimen taken for culture and guinea pig inoculation. Specimens of pus, pleural fluid, urine, gastric contents and others were, as a rule, examined by direct smear once only, and, if found negative, culture and guinea pig inoculation were performed at once. It is very reasonable to assume that, had

TABLE 1

MATERIAL	NEGATIVE		POSITIVE		TOTAL
	Number	Per cent	Number	Per cent	
Sputum	158	61.7	98	38.3	256
Gastric lavage	33	86.8	5	13.2	38
Urine	86	74.1	30	25.9	116
Pleural fluid	19	40.4	28	59.6	47
Pus	10	38.5	16	61.5	26
Miscellaneous	13	62.0	8	38.0	21
Total	319	63.3	185	36.7	504

repeated specimens of these materials been examined by direct smear, tubercle bacilli would have been found in a certain proportion, and the material finally submitted for culture and guinea pig inoculation would have been less often positive.

The effectiveness of repeated direct smears as a means of discovering tubercle bacilli, and thus sparing the laboratory the burden of more complicated methods of search, is illustrated very well in the case of sputum, by comparing the percentage of positive results during the periods 1928 to 1930, 1931 to 1934 and 1935 to 1938 (table 2).

During the last period, the number and frequency of direct smears done on apparently negative cases at the National Jewish Hospital has been greatly increased. The percentage of positive cases, among all the sputa studied by culture and guinea pig inoculation, has shown a marked drop—from 42.1 per cent during the 1928–1930 period, and 47.1 per cent

during the 1931–1934 period, to 15.4 per cent during the period between 1935 and 1938. In other words, almost 85 per cent of the sputum specimens judged negative after thorough examination by direct smear remained negative after the most sensitive methods available were used as a check. During the 1928–1930 period, only 57.9 per cent of specimens negative by direct smear were found negative by culture and guinea pig inoculation.

Among the material other than sputum and gastric contents, the percentage of positives has shown a much smaller drop than among sputa (table 2). During the 1928–1930 period, this percentage was 41.9 per cent, during 1931–1934 it was 39 per cent and during 1935–1938, 34.9 per cent. This relative fixation is ascribable to the fact that the direct smear was not used nearly as frequently in this material as in sputum, and that there was little change in this practice during the past ten years.

TABLE 2

YEARS	SPUTUM				OTHERS			
	Negative		Positive		Negative		Positive	
	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent
1928–30	69	57.9	50	42.1	57	58.1	41	41.9
1931–34	45	52.9	40	47.1	28	61.0	18	39.0
1935–38	44	84.6	8	15.4	43	65.1	23	34.9
Total.....	158	61.7	98	38.3	128	61.0	82	39.0

The gastric lavages are excluded from this comparison because the great majority of them (35 out of 38) were performed during the 1935–1938 period, so that a fair comparison is impossible.

Table 3 demonstrates the proportion of positive results obtained by culture, by guinea pig inoculation and by both methods simultaneously. It is shown that, of 185 positive specimens, 106 (57.3 per cent) were positive by both culture and guinea pig inoculation; 10 (5.4 per cent) by culture alone, and 69 (37.3 per cent) by guinea pig alone. This indicates a considerable preponderance in favor of guinea pig inoculation as the more sensitive method of examination, a conclusion well illustrated in the last line of table 5.

In that table, the total number and total percentage of positive results for each method are given, with those cases positive by both methods listed in both columns. Examination of this table reveals that out of 185

positive specimens, 116 were positive on culture. The latter figure represents 23 per cent of all specimens examined, and 62.7 per cent of the total number of positives; 175 specimens were positive by means of guinea pig inoculation, representing 34.7 per cent of the entire material examined, and 94.6 per cent of the total number of positive specimens.

For sputum the guinea pig is apparently the better method of demonstrating the presence of tubercle bacilli. How much better, can be realized when we find that the positive cultures amounted to 54.1 per cent of all positives among sputum, the positive guinea pigs to 93.9 per cent. Similar analysis yields, for urine, 80 per cent of total positives found by culture, 100 per cent by guinea pig; for pleural fluid, 67.9 per cent by culture, 96.4 per cent by guinea pig; for pus 62.5 per cent by culture, 93.7 per cent by guinea pig; and for the miscellaneous group,

TABLE 3

MATERIAL	CULTURE POSITIVE GUINEA PIG POSITIVE		CULTURE POSITIVE GUINEA PIG NEGATIVE		CULTURE NEGATIVE GUINEA PIG POSITIVE		TOTAL
	Number	Per cent	Number	Per cent	Number	Per cent	
Sputum	47	48.0	6	6.1	45	45.9	98
Gastric lavage	3	60.0	1	20.0	1	20.0	5
Urine	24	80.0			6	20.0	30
Pleural fluid	18	64.3	1	3.6	9	32.1	28
Pus	9	56.2	1	6.3	6	37.5	16
Miscellaneous	5	62.5	1	12.5	2	25.0	8
Total	106	57.3	10	5.4	69	37.3	185

75 per cent of total positives revealed by culture, 87.5 per cent by guinea pig. Only among the gastric lavages did culture seem to keep pace with guinea pig inoculation, with 80 per cent for each; but the total number of positives is so small that these figures are not very significant.

By calculations based on the figures in tables 1 and 3, the percentage of positive specimens, compared to the total specimens, for each type of material, and for each method of examination, can be determined. However, such calculations would lead to conclusions similar to those already drawn, and are therefore omitted.

In table 4 the material studied is divided into three chronological groups corresponding to major changes in technique occurring at the beginning of each period. It will be seen that the percentage of positive specimens remained unchanged to any significant degree during the first

two periods, but showed a considerable drop during the last period. In table 2, it has been shown that the major part of this drop is due to a decrease in the percentage of positive sputa, a smaller part due to a drop in the percentage of positives among other materials. The reasons for this decrease have been discussed previously. The remainder of table 4 does not require analysis, and is inserted only because the figures found there serve as the basis of table 5.

In table 5 are shown the absolute numbers and the percentages of

TABLE 4

YEARS	NEGATIVE		POSITIVE		DISTRIBUTION OF POSITIVE CASES									TOTAL
					Culture positive Guinea pig positive			Culture positive Guinea pig negative			Culture negative Guinea pig positive			
	Number	Per cent	Number	Per cent	Number	Per cent of positive	Per cent of total	Number	Per cent of positive	Per cent of total	Number	Per cent of positive	Per cent of total	
1928–30	127	58.2	91	41.8	52	57.1	24.0	2	2.2	1.0	37	40.7	16.8	218
1931–34	75	56.4	58	43.6	31	53.4	23.3	5	8.6	3.6	22	38.0	16.5	133
1935–38	117	76.4	36	23.6	23	63.9	15.0	3	8.4	1.9	10	27.7	6.7	153
Total...	319	63.3	185	36.7	106	57.3	21.0	10	5.4	2.0	69	37.3	13.7	504

TABLE 5

YEARS	CULTURE POSITIVE			GUINEA PIG POSITIVE			TOTAL CASES	TOTAL POSITIVE
	Number	Per cent of positive	Per cent of total	Number	Per cent of positive	Per cent of total		
1928–30	54	59.3	25.0	89	97.8	40.8	218	91
1931–34	36	62.0	26.9	53	91.4	39.8	133	58
1935–38	26	72.3	16.9	33	91.6	21.7	153	36
Total.....	116	62.7	23.0	175	94.6	34.7	504	185

specimens positive by cuture and by guinea pig, respectively, during the three chronological periods described in table 4. It will be seen that the guinea pig was superior to the culture at all times. The increasing proportion of the total positive specimens revealed by culture indicates that culture methods have improved steadily. This is all the more evident, when it is remembered that the specimens examined contained, on the average, fewer bacilli, during the later years.

It will be noted, also, that the difference between the percentage of

positive specimens found by guinea pig inoculation and by culture has grown smaller steadily. The superiority of the guinea pig is, however, maintained. Over the entire ten-year period, culture yielded positive results in 23 per cent of all specimens; guinea pig in 34.7 per cent. Of all positives obtained, 62.7 per cent were found by culture, and 94.6 per cent by guinea pig inoculation.

SUMMARY AND CONCLUSIONS

1. Guinea pig inoculation was superior to culture as a means of demonstrating tubercle bacilli in all sorts of material.

2. With improvement in culture technique, the gap between these two methods of examination has decreased.

3. A few specimens negative by means of guinea pig inoculation were positive by culture.

4. An increase in the number of direct smears performed before resort to culture or guinea pig inoculation resulted in an increase in the percentage of specimens remaining negative after these more sensitive methods were used. This was true particularly of sputum, which was examined by direct smear much more frequently than other material. It would seem that a good many cultures and guinea pig inoculations might be made unnecessary, if this practice were extended to urines, pus from draining sinuses, and other materials easily available for repeated examination.

5. The best procedure for demonstrating tubercle bacilli in suspected material would seem to be: (*a*) repeated direct smears, as frequently as circumstances permit; (*b*) one or more cultures, if smears are persistently negative; (*c*) guinea pig inoculation of all material negative by culture.

6. No case should be considered negative until all means of examination have repeatedly failed to demonstrate tubercle bacilli in the suspected material. The exact number of examinations necessary depends on the individual case.

REFERENCES

(1) Corper, H. J.: J. A. M. A., 1928, *91*, 371.
(2) Corper, H. J., and Uyei, N.: J. Lab. & Clin. Med., 1929, *14*, 393.
(3) Corper, H. J., and Uyei, N.: Ibid., 1930, *15*, 348.
(4) Corper, H. J., and Cohn, M. L.: Am. J. Hyg., 1933, *18*, 1.
(5) Norton, J. F., Thomas, J. G., and Broom, N. H.: Am. Rev. Tuberc., 1932, *25*, 378.
(6) McNabb, A. L., and Wilson, W. M.: Canad. Pub. Health J., 1932, *23*, 284.
(7) Mishulov, Romano, Melman and Kereszturi: J. Infect. Dis., 1934, *55*, 402.
(8) Frankl, L.: Schweiz. med. Wchnschr., 1934, *2*, 1191.

(9) Limito, C.: Osp. Magg. (Milano), 1935, *23*, 433.
(10) Ruys, A. C.: Nederl. Tijdschr. Geneesk., 1938, *82*, 18.
(11) Schnittler, K.: Sonderbeil. d. med. Rev., 1937, *3*, 93.
(12) DeGironcoli, F., and Bartolozzi, M.: Urologica, 1937, *4*, 24.
(13) Paponnet: Arch. Med. Nav., 1936, *126*, 5.
(14) Stadnichensko, A., and Sweany, H. C.: Am. J. Clin. Path., 1931, *1*, 303.
(15) Farjot, A.: Compt. rend. Soc. de biol., 1933, *113*, 770.
(16) Blair, J. E., and Hallman, F. A.: Arch. Surg., 1933, *27*, 178.
(17) Ronzini, M.: Riforma med., 1931, *2*, 1183.
(18) Graziosi, G.: Riv. di pat. e clin. d. tuberc., 1934, *8*, 157.
(19) Blanco, R. F.: Archivos tuberc., 1933, *1*, 151.
(20) Holst, P. M.: Norsk. Mag. Laegevidensk., 1934, *95*, 958.
(21) Levin, N.: Acta paediat., Suppl. 1, 1935, *17*, 160.
(22) Daddi, G.: Lotta contro la tuberc., 1935, *6*, 577.
(23) Gelberg, S., Frumkina, G., Danovic, S., and Rachmancik, G.: Bor'ba tuberk., 1935, *1*, 18.
(24) Natin, I.: Semana méd., 1937, *2*, 306.
(25) Saenz, A., and Costil, L.: Compt. rend. Soc. de biol., 1933, *113*, 50.
(26) Magath and Feldman: Am. J. Clin. Path., 1932, *2*, 199.

TUBERCULOSIS SURVEY IN FLORIDA[1]

ARTHUR J. LOGIE

In 1937 the first centralized attack upon the problem of tuberculosis control was launched by the newly created Division of Tuberculosis of the Florida State Board of Health. A state-wide antituberculosis program was inaugurated with the approval of the State Medical Association. The inauguration of the program coincided with the opening of the first and only State sanatorium. The case-finding feature of the program served as a survey of the incidence of tuberculous infection. The groups selected for the investigation were indigent contact and suspected cases of tuberculosis referred by health officers and local physicians, and senior high school and freshmen college students.

FIELD OF SURVEY

During the period from June, 1937 to June, 1938, the selected groups in ten counties of the State were tuberculin tested and the positive reactors were X-rayed. The counties chosen for the investigation have a scattered geographical distribution and represent a well balanced cross section of the population of the State. The selection was based chiefly upon the existence of an organized health department in the county so that satisfactory coöperation could be expected and efficient follow-up work assured. The ten counties represent a balanced socio-economic group, mixed rural and urban areas, and they have an average tuberculosis mortality rate closely approximating the average for the entire State. The possibility of the statistical findings being influenced by the large nonresident population in the winter resort areas was avoided by introducing the program in these areas during the off season of the year.

PLAN OF SURVEY

The personnel of the Division of Tuberculosis consists of a director, a tuberculosis nurse, an X-ray technician and a secretary. As funds

[1] From the Division of Tuberculosis, State Board of Health, Jacksonville, Florida.

available to the Division were limited, the firm coöperation of the State Tuberculosis Association enabled an intensive publicity campaign to be launched. The following routine method of approach to each county was established:

Each county was scheduled for the tuberculin tests and for the X-ray studies six months in advance. A series of lectures and demonstrations, and the distribution of literature dealing with the various aspects of tuberculosis enlisted the support of the medical society. Personal conferences and talks to the county educational authorities, school principals and teachers promoted good will and the desire to assist in the program. Discussions, moving pictures on tuberculosis and assorted literature created enthusiasm for the program among lay organizations. Lectures to nurses and instructions to health departments prepared an organized local personnel.

Two months prior to the date scheduled for local inauguration of the program, the State tuberculosis nurse contacted the public health and WPA nurses in the county and explained, in detail, the routine which was to be followed. They were given slips which they distributed to the senior high school and freshmen college students (consent slips), and to local physicians, health clinics and social welfare agencies (request slips). The student under eighteen years of age had to return the consent slip completely filled in and signed by a parent. The request slips were used only for indigent contact or suspected cases. An ample supply of both types of slips was left with the local health departments. Health authorities were advised to investigate the contacts of those cases which had died of tuberculosis or which had been reported as sick with it within the past three years. If indigent, these individuals were listed at clinics and were included in the program, providing request slips had been signed by local physicians. After these preliminaries had been arranged and organized the schools and clinics were placed on schedule for tuberculin testing.

One month prior to the date scheduled for testing, the X-ray technician visited the county and selected suitable centres for the X-ray work. The electric current was checked and arrangements were made with the power supply company for alterations or additions to avoid line current fluctuations and to insure satisfactory energizing of the X-ray apparatus. The technician explained, in detail, the local organization necessary for the X-ray program to the workers and gave them pamphlets outlining

their individual duties. Suitable centres having been selected, arrangements were made with the county authorities for those who were to be X-rayed to be transported in buses on the dates scheduled.

Upon the dates scheduled for tuberculin testing, the director of the Division visited the selected schools and clinics in the county and gave the tests. Individuals were tested at the rate of 100 per hour. The reactions were read by the director and were recorded on the person's consent or request slip. After the tests had been read the students and the contact cases were advised of the time and places where the X-ray films of the positive reactors would be made.

Approximately one month following the giving of the tests, the X-ray work began. The positive reactors were arranged in lines according to height so that the speed of operating the X-ray unit would not be reduced by frequent changes in the level of the cassette box. The Powers rapid X-ray unit with paper film in rolls and a moderately high-powered X-ray machine were employed. The equipment was transported from place to place in a specially built truck and was unloaded and set up in the centres previously designated for the X-ray work. The rapid unit permitted approximately 75 to 100 individuals to be radiographed in one hour. Single flat films with the subject in the posteroanterior position were made. After several paper rolls had been exposed, they were shipped in metal containers to the manufacturers in New York for developing. Within two weeks they were returned ready for interpretation by means of a special viewing cabinet.

All plates were interpreted according to generally accepted standards by the director and the findings marked directly on the film. The X-ray findings were also recorded on the consent and request slips. All information derived from the slips including the tuberculin reaction and X-ray finding was then recorded on special forms for the office files. After this was done, the consent and request slips were returned to the county health officer for distribution to the family physician mentioned on the face of each slip. Indigents professing no family physician were followed-up by the local health officer. When the family physician received these slips, he also received a circular letter recommending the follow-up work which should be done; such as annual retesting of negative reactors, repeated X-raying of positive reactors, tracing the source of infection in the family and the immediate treatment and isolation of the cases showing reinfection type tuberculosis.

In order to avoid placing the stigma (unfortunately still prevalent in

certain circles) of a diagnosis of pulmonary tuberculosis upon a person showing primary infection, the condition was generally reported, "no manifest active pulmonary tuberculosis." Along with the routine report, in the case showing a reinfection type lesion, the family physician received a detailed description of the X-ray appearance and suggestions of the type of treatment (observation, investigation for activity, sanatorium confinement, pneumothorax therapy, etc.). For the convenience of the physician, a form was included which he might send to parents of the child or directly to the patient, if an adult, requesting a visit to his office so that he might explain in a satisfactory manner the reports he had received. Three months after the reports had been sent to the family physician, he was requested to notify the county health officer of the follow-up work which had been done and of the disposition made of the case.

STATISTICAL RESULTS

Table 1 shows the frequency of positive tuberculin reactors in the white and Negro by age. All tests were done with PPD (two strengths). In all, 12,866 persons were given intracutaneous tests, of which 32.7 per cent reacted. This percentage compares favorably with the incidence of positive reactors (39.3 per cent) for all ages in the South Atlantic States during 1934–1936 (1). In each age group over five years the percentage of Negro reactors was higher than the percentage of the white. Although, in Florida, the Negro tuberculosis death rate is three and one-half times that of the white, the ratio of the incidence of Negro reactors to white was only 1.4 to 1. The high incidence of reactors among children under five years was due to the fact that all had been in contact with cases of tuberculosis at home. Among all adults twenty-five years and over, 59.3 per cent had positive reactions. The tuberculin test in adults is taking a more important rôle than formerly when 80 to 100 per cent of them showed reactions. This group consisted chiefly of school teachers, other school employees and a number of individuals reported as possible contacts. The adolescent group consisted of senior high school and freshmen college students. As the difference in the incidence of infection between the sexes has been found insignificant, no distinction was made (2).

Table 2 is a comparison of the percentages of reactors, white and Negro, by age in Florida with recent findings in Lee County, Alabama and with the average for the entire country in 1934–1936. In the Florida

group, there was included a relatively large number of persons reported as possible contacts. This should raise the rates, in all age groups above those usually found in the general population. Notwithstanding, the

TABLE 1

Frequency of positive reactors in Florida by age and color (intracutaneous test with two strengths PPD)

AGE	WHITE		NEGRO		TOTAL	
	Number tested	Positive	Number tested	Positive	Number tested	Positive
years						
0–4	38	19 (50%)	25	12 (48%)	63	31 (49.2%)
5–9	262	57 (21.8%)	181	46 (25.4%)	443	103 (23.3%)
10–14	1,981	502 (25.3%)	637	219 (34.4%)	2,618	721 (27.5%)
15–19	6,313	1,821 (28.8%)	1,771	714 (40.3%)	8,084	2,535 (31.4%)
20–24	422	149 (35.3%)	476	212 (44.5%)	898	361 (40.2%)
25 and over	471	249 (52.9%)	289	202 (69.8%)	760	451 (59.3%)
Total.....	9,487	2,797 (29.5%)	3,379	1,405 (41.6%)	12,866	4,202 (32.7%)

TABLE 2

Percentage incidence of positive reactors in Florida, in Lee County, Alabama and in the United States

AGE	WHITE			NEGRO		
	Florida	Lee County	United States	Florida	Lee County	United States
years						
5–9	21.8	41.9	17.1	25.4	34.4	25.1
10–14	25.3	57.7	24.2	34.4	52.4	36.4
15–19	28.8	72.2	28.4	40.3	67.0	41.6
20–24	35.3	80.9	55.2	44.5	75.1	59.1
25 and over	52.9	83.7		69.8	84.7	

Florida percentages, for all age groups over five years, were considerably lower than those found in a recent survey of Lee County, Alabama (3), and much the same as the averages for the United States as a whole (1).

Table 3 shows the relationship between the tuberculin tests (PPD) and the X-ray findings. The percentage of reactors to the first strength was 7.5 per cent and of the 11,900 individuals who did not react to first strength, 3,236 (27.1 per cent) reacted to the second strength. The

TABLE 3

Relation between tuberculin tests and X-ray findings

TEST	NUMBER TESTED	POSITIVE	X-RAYED	NEGATIVE	CALCIFIED FOCI	LATENT APICAL LESIONS	MANIFEST PULMONARY TUBERCULOSIS	TOTAL TUBERCULOUS LESIONS
1st PPD	12,866	966 (7.5%)	631 (65.2%)	440 (69.7%)	170 (26.9%)	13 (2.06%)	8 (1.26%)	191 (30.3%)
2nd PPD	11,900	3,236 (27.1%)	2,437 (75%)	1,931 (79.2%)	470 (19.2%)	29 (1.19%)	7 (0.28%)	506 (20.8%)
Total.....		4,202 (32.7%)	3,068 (73%)	2,371 (77.2%)	640 (20.8%)	42 (1.37%)	15 (0.48%)	697 (22.3%)

TABLE 4

Frequency of tuberculous lesions (X-ray survey) by age

AGE	NUMBER X-RAYED	NEGATIVE	CALCIFIED FOCI	LATENT APICAL LESIONS	MANIFEST PULMONARY TUBERCULOSIS	TOTAL TUBERCULOUS LESIONS
years						
0–4	38	29 (76.3%)	9 (23.7%)	0	0	9 (23.7%)
5–9	131	111 (84.7%)	18 (13.7%)	2 (1.5%)	0	20 (15.3%)
10–14	693	558 (80.5%)	129 (18.6%)	6 (0.9%)	0	135 (19.4%)
15–19	2,328	1,933 (83%)	388 (16.7%)	7 (0.33%)	0	395 (17%)
20–24	329	240 (73%)	75 (22.8%)	11 (3.3%)	3 (0.9%)	89 (27.1%)
25 and over	431	236 (54.7%)	152 (35.3%)	22 (5.1%)	21 (4.9%)	195 (45.3%)
Total.....	3,950	3,107 (78.6%)	771 (19.3%)	48 (1.2%)	24 (0.61%)	843 (21.1%)

percentage reacting to the first PPD is much lower than that found in other surveys (4, 5). The incidence of demonstrable tuberculous lesions among the reactors is summarized in table 3. Many workers have found that persons with clinically significant chest lesions usually react to the

first strength PPD (4, 6). Our findings show that 36 individuals with clinically significant lesions reacted only to the second strength. Of 4,202 total reactors, 3,068 (73 per cent) appeared for X-ray examination. The percentage of lesions in our reactors is higher than usual because of the greater percentage of cases from contact homes. Of all reactors X-rayed 1.85 per cent had reinfection type tuberculosis, and 1.37 per cent were latent apical lesions of suspicious tuberculous origin. A higher percentage of cases with the reinfection type was found in persons reacting to the first strength (3.32 per cent) than in those reacting to the second PPD (1.47 per cent).

In all, 3,950 individuals were X-rayed, of which 3,068 were positive tuberculin reactors and 882 persons who had not been tested. The

TABLE 5

Frequency of tuberculous lesions of those reported as contacts, by age

AGE	NUMBER X-RAYED	NEGATIVE	CALCIFIED FOCI	LATENT APICAL LESIONS	MANIFEST PULMONARY TUBERCULOSIS	TOTAL TUBERCULOUS LESIONS
years						
0–14	312	232 (74.2%)	75 (24%)	5 (1.6%)	0	80 (25.6%)
15–24	130	92 (70.7%)	28 (21.5%)	6 (4.7%)	4 (3.1%)	38 (29.3%)
25–44	126	70 (55.6%)	35 (27.8%)	11 (8.7%)	10 (7.9%)	56 (44.4%)
45 and over	43	19 (44.2%)	13 (30.2%)	6 (13.9%)	5 (11.7%)	24 (55.8%)
Total.....	611	413 (67.6%)	151 (24.7%)	28 (4.6%)	19 (3.1%)	198 (32.4%)

latter were included upon the request of local physicians because of symptoms referable to the chest. Table 4 shows the frequency of tuberculous lesions by age in those who were X-rayed. Of the children under five years of age, including the 31 tuberculin-positive contact cases (table 1), none had any active lesions manifest by X-ray, although 23.7 per cent had calcified foci. In view of the fact that it takes two to four years for calcification to become manifest radiographically (7), it appears likely that infection in these young contacts occurred in the interval between early infancy and three years of age. All children under five years of age with positive tuberculin reactions are being followed closely. The other members of the households are being investigated at the time of this writing.

Table 5 represents the frequency of tuberculous chest lesions on X-ray by age groups of those who were reported as contacts. Of 611 contacts (15.5 per cent of total X-rayed), all ages, 4.6 per cent had latent apical lesions of which the highest percentage was found in adults forty-five years and over (13.9 per cent), and 3.1 per cent had manifest tuberculous lesions of which the highest percentage was found in those over forty-five years (11.7 per cent). It is apparent that active tuberculosis occurs more frequently in older adults than has been generally recognized. In each age group the percentage of tuberculous lesions was considerably higher than that found in table 4.

TABLE 6

Incidence of tuberculous lesions in contacts and in those in whom no contact was reported (all ages combined)

	NUMBER X-RAYED	NEGATIVE	CALCIFIED FOCI	LATENT APICAL LESIONS	MANIFEST PULMONARY TUBERCULOSIS	TOTAL TUBERCULOUS LESIONS
		per cent	*per cent*	*per cent*	*per cent*	*per cent*
Cases reported as contacts	611	67.6	24.7	4.6	3.1	32.4
Cases not reported as contacts	3,339	80.7	18.5	0.59	0.15	19.3
All cases	3,950	78.6	19.3	1.2	0.61	21.1

TABLE 7

Cases of reinfection type tuberculosis

TOTAL	MINIMAL	MODERATELY ADVANCED	FAR ADVANCED
72	56 (77.8%)	11 (15.3%)	5 (6.9%)

In table 6, from the comparison of X-ray findings in those reported as contacts with those in which no contact had been reported, it is evident that among the former the percentage of demonstrable chest lesions was 1.6 times greater, of calcified foci 1.3 times greater, of latent apical lesions 7.6 times greater, and of manifest tuberculous lesions 20 times greater than the percentage of those with similar lesions among cases in which no contact had been reported.

Table 7 shows a total of 72 cases diagnosed by means of the tuberculin test and/or the X-ray of which 56 (77.8 per cent) were in the minimal stage, 11 (15.3 per cent) in the moderately advanced stage, and 5 (6.9 per cent) in the far advanced stage. Reinfection type lesions were found

in 1.85 per cent of the tuberculin reactors, in 1.81 per cent of all persons X-rayed, in 7.7 per cent of those cases reported as contacts and in 0.74 per cent of those cases in which no contact was reported.

CONCLUSION

As the relationship between the intensity of the reaction and the degree of tuberculous activity, the time of infection, or the clinical course which the disease will pursue has not been proved, it was not considered necessary to classify the degree of the reactions. There seemed to be a distinct relationship between the size of the reaction and the amount of PPD injected, particularly in the younger children tested (8).

Of all the positive tuberculin reactors, 10 per cent consisted of adults over twenty-five years of age. The fact that the great majority of them reacted to the second dose of PPD, contributed to the low percentage of reactors to the first strength PPD. This is to be expected in view of the fact that, as calcification and healing occur, there is a decrease in the allergic response.

The great majority of the tests were given by one individual trained in the work. The personal equation of differences in interpreting reactions was a very small factor as 93 per cent of the test readings were made by a single person. To be called positive, a reaction had to show, after forty-eight hours, induration measuring at least 5 mm. in its shortest diameter.

The possibility of the first test causing a reawakening of allergy so that those who were negative to the first reacted to the second test does not appear likely as the second PPD, in the great majority of cases, was administered forty-eight hours after the first test, and in no case later than seven days afterward. A few children tested in this survey had been reactors to a test done the year previous. Several of them had reactions accompanied by an erythematous flare-up at the site of the previous test in the other forearm.

We believe with Myers that the best criterion of the tuberculosis problem in the State is the incidence of positive tuberculin reactors rather than morbidity and mortality rates. In the field of public health, Florida must be considered a pioneer State. Until quite recently little confidence could be placed in mortality and morbidity statistics as an accurate index of the tuberculosis problem in the State. In the past, the statute making notification of cases of the disease compulsory has neither been observed nor enforced.

We rent the rapid X-ray unit and purchase paper film in rolls. The unit is operated by the X-ray technician on our staff. We have found

the rapid unit and paper film admirably suited to our case-finding program. It has proved to be economical both in time and money, permitting large groups to be radiographed in relatively short intervals at a comparatively low cost. The films have been uniformly developed and no more difficult to read than celluloid films. When reporting cases with reinfection type lesions, we had advised the family physicians to make further X-ray studies of the cases. When comparisons were made between the celluloid and the paper films, in each case the celluloid confirmed the diagnosis made on the paper film. In several cases the celluloid film brought out more clearly subminimal shadows at the apices of the lung which had been seen on the paper film as suspicious infiltrations; but, in these cases, the obscurity was generally caused by the poor positioning of the patient which was due, in part, to the rapid technique used and, in part, to the lack of coöperation of some of the persons X-rayed. There was a 6.6 per cent X-ray loss due chiefly to fluctuation of line current. The unsatisfactory plates were repeated and by checking the power with a voltmeter, by having the local power supply companies drop transformers nearer the X-ray set-up, and by reducing the speed of operation from 100 to 75 X-ray exposures per hour, further loss was prevented and clearer apices obtained on the films.

The plan of the program resembled the scheme used in the State of Connecticut several years ago. The program has proved to be an efficient case-finding medium. Although the cases discovered were relatively few in number, in the great majority of them the prognosis was favorable because of the early diagnosis of the condition in the minimal stage. The program has augmented and materially assisted the work of the county health unit and has encouraged the inauguration of local antituberculosis programs. It has been of great value and of mutual benefit to the patient and to the physician in general practice. It has stressed the important rôle of the family physician and the roentgenologist in the prevention of tuberculosis. It has aroused great interest among the laity and has served as an excellent means of health education. It has combined the individual efforts of the State Medical Society, the State Tuberculosis Association and the State Board of Health and has merged them into a concerted attack upon the tuberculosis problem in Florida. The program will be continued among contacts and probably extended to include inmates of custodial institutions, certain industrial groups, persons who are unemployed and a greater proportion of the Negro population.

SUMMARY

1. The case-finding feature of the Florida Antituberculosis Program, including a tuberculosis survey of senior high school and freshmen college students, is described in detail.

2. The frequency of positive reactors by age and color in 12,866 individuals tested with PPD is presented.

3. The relationship between the tuberculin test and the X-ray findings and the incidence of demonstrable tuberculous lesions in 3,950 individuals and 611 contacts radiographed is tabulated.

4. Of 72 cases with reinfection type lesions uncovered by means of the program, 77.8 per cent were in the minimal stage.

5. The value of the rapid X-ray unit with paper film in rolls is stressed.

REFERENCES

(1) WHITNEY, J. S., AND MCCAFFREY, I.: Final report on PPD, Am. Rev. Tuberc., 1937, *35*, 597.

(2) DROLET, G. J.: The incidence of tuberculous infection among children in New York City, Ibid., 1934, *30*, 1.

(3) Tuberculosis Survey, Lee County, Alabama, presented by U. S. P. H. S. at the annual meeting of the National Tuberculosis Association in Los Angeles in June, 1938.

(4) NOVAK, J. B., AND KRUGLICK, J. S.: Tuberculosis survey in Chicago high schools, Am. Rev. Tuberc., 1938, *38*, 106.

(5) CRIMM, P. D., SHORT, D. M., AND WOOD, H. E.: Evaluation of OT and PPD with X-ray correlation, Tr. Nat. Tuberc. A., 1937, p. 120.

(6) LONG, E. R., AND SEIBERT, F. B.: Further studies on PPD, Am. Rev. Tuberc., 1937, *35*, 281.

(7) CHADWICK, H. D.: Tuberculosis in children and adolescents, Michigan State M. J., 1932, *31*, 112.

(8) LINCOLN, E. M., RAIA, A., AND GILBERT, L. A.: Tuberculin reactions in children, J. Pediat., 1938, *12*, 484.

INDUSTRIAL DUSTS AND THE MORTALITY FROM PULMONARY DISEASE[1]

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Air and water are the two immediate vital necessities of our lives. We take extraordinary precautions to guarantee for ourselves not only an ample supply of water but one of defined purity, and vast engineering water-supply projects, costing many millions of dollars, are an accepted and commonplace fact in our times.

With respect to the air we breathe, we are more complaisant. Dust arising from industrial processes pollutes the atmosphere of working places, in mine, factory and mill, and the products of combustion, both industrial and nonindustrial, are liberated into the atmosphere of our communities with little restraint. In recent years, particularly, industrial dusts have received much attention and much effort has been put forth by industrial firms of all kinds to control dusty processes in their establishments.

Fortunately, nature has furnished us with a respiratory system which has not only a large margin of safety, but a fairly efficient protective mechanism. When that protective mechanism is subjected to severe stress for a sufficiently long period of time, it may fail. The extent to which such failure may be reflected in mortality experience is, within certain limitations, the subject of this discussion.

We are concerned here with industrial dusts other than those commonly recognized as poisonous. Lead, mercury, arsenic, manganese and other systemic poisons are excluded, together with the chemical poisons. Those dusts with which we are concerned are both organic and inorganic, and the latter, in turn, may be subdivided into metallic and nonmetallic. There are many possible subdivisions of these three classifications but for our purpose extensive subdivision is unnecessary. Indeed, it is difficult to get sufficiently ample statistical material to give us definite information under the general headings.

[1] Read as part of the Symposium on *Tuberculosis in Industry* at the joint session of the Pathological, Clinical, Social Work and Administrative Sections at the 34th annual meeting of the National Tuberculosis Association, Los Angeles, California, June 23, 1938.

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In 1908, Dr. Frederick Hoffman (1) wrote an article on the mortality from consumption in the dusty trades. Ten years later, he produced the well known Bulletin 231, *The Mortality from Respiratory Diseases in the Dusty Trades* (2), an important milestone in the hygiene of industry. In 1919, appeared the first and second preliminary reports of the Committee on Mortality from Tuberculosis in the Dusty Trades (3), of which Committee, Doctor Hoffman was Chairman. An indefatigable worker in many fields of public health, Doctor Hoffman's name is thus linked to the early authoritative publications in this country dealing with dust and pulmonary disease. The various reports of Governmental Commissions in South Africa, Australia, Great Britain and other countries have also stimulated industrial studies and laboratory research into the effects of many kinds of industrial dusts, especially those containing silica.

At the present time, while no one would state that we have adequate information about the effects of the inhalation of industrial dusts, we do know a great deal more than we did twenty years ago. Both clinical and laboratory studies have given us some knowledge of what kinds of dusts are dangerous, the circumstances under which they are dangerous, and the nature of their action upon the pulmonary tissue. We have also learned a great deal about the prevention and control of the dust hazard by engineering methods. But when we seek evidence of the effects of dust inhalation in mortality and morbidity records, we find that the statistical demonstration of mortality and morbidity due to the inhalation of dusts is anything but satisfactory or complete.

This situation is the more regrettable because comprehensive mortality and morbidity statistics would be of the greatest value in clearing up many doubtful points regarding the effects of specific dusts and would bring to light occupations in which there might be a real, but unsuspected, exposure to injurious dusts. Early occupational mortality studies, it must be admitted, gave the first broad clues to the extent of the dust hazard in industry and to the kinds of dust which are most injurious. These earlier mortality studies, valuable as they were, however, were in many instances misleading. Virtually all kinds of dusts were shown to be productive of tuberculosis rates higher than average, whereas recent clinical and laboratory experience points to the very considerable damage to the lung tissue produced by a few dusts, notably silica and asbestos, and to the relatively little evidence of harm done to the lung tissue by organic and many inorganic dusts.

There are reasons, obvious to us to-day, why these mortality studies have not been an entirely accurate guide. For one thing, students of mortality did not have the benefit of the clinical and laboratory knowledge regarding dusts now available and, consequently, had to make their own classifications of dusts on a somewhat arbitrary basis. They were handicapped, too, by the fact that the existing occupational codes often brought together all the men in a whole industry. This did not permit of detailed studies of the mortality of men exposed to a single type of dust. Occupational mortality statistics still lose much of their value because of this same lack of refinement in methods of classifying occupations. Then again, factors other than dust, which have a marked influence upon the incidence of tuberculosis among men engaged in different occupations, were not as well understood and were not given due consideration in interpreting the results of mortality studies.

There are pitfalls in reasoning from cause to effect, especially where tuberculosis is concerned, and the error of *post hoc ergo propter hoc* is particularly to be guarded against. A high incidence of tuberculosis or other respiratory disease among men in a given occupation does not necessarily indicate the existence in that occupation of a definite occupational hazard. It is well established that people of the poorer economic classes, whether in industry or out of it, have a higher incidence of respiratory tuberculosis than do people better off financially. In Miss Whitney's (4) study of *Death Rates by Occupation in Ten States in 1930,* the standardized death rate for tuberculosis was over twice as high among unskilled workers as among all occupied males while in the Registrar-General of England and Wales' study (5), 1921–1923, the rate for unskilled workers was about two-fifths higher than the rate for all occupied and retired civilian males. Certain occupations, too, are more suited to the physically weak and are selected by them as a means of earning a livelihood. When the followers of an occupation are recruited from the ranks of either of these classes, it is to be expected that a high r incidence of tuberculosis mortality will be found among them. Failure to take cognizance of these factors as possible explanations of a high tuberculosis incidence in certain callings has led to much misinterpretation of the significance of mortality findings.

It is not our purpose to reassess the older statistical material to which reference has been made. We shall limit our discussion of statistics mainly to the results of the three most recent investigations in which tuberculosis death rates are obtainable for a number of occupations.

These are the Registrar-General's Decennial Supplement for England and Wales (5) and two studies made jointly by the Actuarial Society of America and the Association of Life Insurance Medical Directors (6, 7).

In the English study, the tuberculosis death rate for men in a given occupation, ages 20 to 65 years, is compared with that for all occupied and retired civilian males of the same ages. The method of analysis employed in the insurance studies was to compare the actual number of deaths which occurred among men engaged in a specific occupation with the expected number of deaths calculated on the basis of death rates by ages prevailing among standard lives, that is, persons who buy insurance on an annual basis in amounts of $1000 or more and who are not employed in hazardous occupations. Thus the insurance standard is a more rigorous one than that of "occupied males in the general population" since those in the lowest social-economic class are excluded, as are men who are employed in occupations where there is a serious exposure to dust, accident or other hazards. This should be kept in mind in interpreting the figures presented for insured lives in the following discussions.

INORGANIC DUSTS

Silica: Silica in the form of dust produces a definite, characteristic disease of the lungs, namely silicosis, a progressive fibrosis which, of itself, may cause disability and death and which carries with it a predisposition to tuberculous infection. Silicosis results from the inhalation of dust containing free or uncombined silica. Its pathology has been extensively studied, both clinically and in the experimental laboratory. It has been established that silica particles which penetrate the lungs are under ten micra in their largest diameter and are mostly from one to three micra. Not only must the silica dust be in a state of such fine subdivision, but the particles must be present in large amounts and the exposure of the individual must be prolonged. When such conditions are fulfilled the natural defenses of the body against inhaled dust break down and silicosis results.

The precise nature of the action of silica dust upon body tissues is not definitely known but it appears to be a protoplasmic poison and produces its effect chemically and not mechanically. A given dust is dangerous in proportion to the amount of free silica which it contains. The nature of the relationship between silicosis and tubercle infection has not been determined, but the fact of such relationship is attested by overwhelming evidence both clinical and statistical (8).

No useful purpose would be served by quoting extensively from the impressive volume of mortality data available to show the influence of silica dust on the incidence of tuberculosis. Virtually every one of the many studies is in agreement in showing extraordinarily high mortality rates from tuberculosis for industries and occupations in which large numbers of men are known to be exposed to a real silica hazard. These rates are so high, in fact, as to leave no room for doubt of the cause-and-effect relationship between the hazard and the high mortality. A few figures from the insurance investigations (6, 7) may be quoted. Table 1 shows the ratio of actual to expected deaths for the chief occupations exposed to silica dust.

TABLE 1

Number of deaths and ratio of actual to expected deaths from tuberculosis of the respiratory system

Ordinary Department Mortality Experience of American Life Insurance Companies*

Occupations exposed to silica dust

OCCUPATION	1915–1926		1925–1936	
	Actual deaths	Ratio per cent actual to expected	Actual deaths	Ratio per cent actual to expected
Stonecutters—granite and sandstone	16	976	38	2,639
Chippers of metal—(not shipbuilding)	8	615	16	1,667
Mine operatives—underground				
Copper mine operatives	24	913	29	1,381
Gold and silver mine operatives	9	804	11	940
Iron mine operatives	4	260	12	857
Lead and zinc mine operatives	11	1,833	3	—
Other and not specified mine operatives	†	—	10	1,020

* Compiled from: Joint Occupation Study, Actuarial Society of America and The Association of Life Insurance Medical Directors, 1929; and Occupation Study, Actuarial Society of America and The Association of Life Insurance Medical Directors, 1938.

† Data not available.

Among a group of underground miners employed in mines other than coal mines, nearly all of whom were employed in metal mines, there were 65 deaths from tuberculosis in the years 1925–1936 in an exposure of 25,000 life years where 6 were expected, or about eleven times as many deaths as the expected number. There were 13 deaths from pneumonia where 5 were expected. Tuberculosis deaths were fourteen times the expected among copper miners, nine times the expected among gold and silver miners, and eight and a half times the expected among iron miners. In this experience, there was only a small representation of lead and zinc

miners, but in the earlier study (6), covering the years 1915–1926, there were 11 deaths from tuberculosis in this group or eighteen times as many as expected. The ratio for iron miners, 857 per cent, is unexpectedly high inasmuch as it is thought that most of these workers are exposed to only moderate amounts of silica dust, except for a limited number who are working in hard rock. It might have been expected that their mortality would more closely approximate that of coal miners. The number of deaths is small, however, and the difference may be more apparent than real.

Among cutters of granite and sandstone, there were 38 deaths from tuberculosis in an exposure of 5,944 life years, compared with 1.4 expected, or more than twenty-six times as many as the expected number of deaths. Chippers of metal (exclusive of ship chippers) had 16 deaths from tuberculosis where only one was expected.

It will be observed that the ratio of actual to expected deaths from tuberculosis for each of the silica occupations is higher in the period 1925–1936 than in the period 1915–1926. The reason for this apparently lies in the difference in the trend of the death rates for men in these occupations and the rate for insured persons generally. While the figures are too small on which to base broad conclusions, they suggest that men in silica occupations have not shared in the general decline in the death rate from tuberculosis. It may be that there was actually an increase in the rates for the period 1925–1936 over that for the period 1915–1926.

Interesting confirmation of these high ratios by English data is presented in table 3. English tin and copper miners had a death rate from tuberculosis eleven and one-half times the average; sandstone masons, cutters and dressers, nearly four and one-half times the average; and metal grinders, about three and two-thirds times the average. Ratios such as these cannot be explained away on the ground of differing social classes or the selection of the occupation by physically weaker types of workers.

This evidence is in agreement with reports of silicosis studies from South Africa, Australia, Canada, and Great Britain as well as the United States and is supported by clinical experience of physicians in many parts of the world whose practice has been among workers exposed to silica dust.

Coal dust: It has long been known that coal miners are subject to chronic pulmonary disease characterized by dyspnoea and usually termed "miners' asthma," also that the death rate from respiratory diseases is

high among certain groups of miners while among others the death rate from tuberculosis has been consistently low. Recent investigations have cleared up many points about the hazard of coal dust and have indicated certain differences between anthracite coal and bituminous coal. It is desirable, therefore, in studying the effects of coal dust to consider these two types of exposure separately.

In 1934, the Public Health Service (9) made a report on an investigation of pulmonary disease among anthracite miners. This report stated what had previously been suspected, namely, that anthracite mining had, under certain conditions, a silica hazard and many anthracite miners were exposed to the effects of coal and silica dust. The evidence tends to show that disabling miners' asthma is, in effect, silicosis, a silicosis modified by coal dust but nevertheless a silicosis.

Turning to the mortality record of coal miners, we find that the Medico-Actuarial Occupation Study (7) shows for the Pennsylvania miners (nearly all anthracite) the following figures, based on 144,535 life years, for the twelve-year period 1925–1936: There were 1,699 actual deaths where 613 were expected, giving a ratio of actual to expected deaths of 277 per cent. Of this excess, 37 per cent was due to accidents and 63 per cent to disease. The pneumonia and influenza death rate was five times the normal; tuberculosis, over three times the normal; and accidents, five times the normal.

Miners elsewhere (bituminous) presented the following figures: There were 52,522 life years and 330 actual deaths against 187 expected, a mortality ratio of 176 per cent, but of this excess mortality, 84 per cent was due to accidents and 16 per cent to disease. The death rate from accidents was five times the normal; the pneumonia death rate was normal; and the tuberculosis death rate, 61 per cent in excess of normal.

In the insurance occupation study (6, 7), as we have pointed out, the death rates for each occupation are compared with the rate for standard ordinary policy holders, a rigorous standard as compared with the rate for all occupied males. When considering the mortality of men employed in mining operations many of which are carried on by unskilled workers, it is especially necessary to bear this fact in mind. Apart from any specific occupational influence conducive to a high incidence of tuberculosis, we should expect a greater than average mortality from tuberculosis among them because of their economic status. Insured common laborers outside of the mining industry, it should be mentioned, have a death rate from tuberculosis about three times as great as that of Stand-

ard lives. Compared with the death rate for laboring groups generally, therefore, the tuberculosis rate for bituminous miners is quite low, whereas the rate for anthracite miners is as high, if not actually higher, than the average for this class of workers. The number of deaths and the ratio of actual to expected deaths for coal miners is given in table 2.

The following quotation from the Public Health Service report (9), previously referred to, is of interest in showing the incidence of clinical tuberculosis among anthracite miners:

Several surveys have shown that tuberculosis of the lungs occurs among 1 to 2½ per cent of the general adult white male population of the country. In a

TABLE 2

Number of deaths and ratio of actual to expected deaths from tuberculosis of the respiratory system

Ordinary Department Mortality Experience of American Life Insurance Companies*

Coal Miners

OCCUPATION	1915–1926		1925–1936	
	Actual deaths	Ratio per cent actual to expected	Actual deaths	Ratio per cent actual to expected
Operatives not underground	14	159	†	—
Operatives underground				
Total	125	157	135	288
Pennsylvania (mostly anthracite)	†	—	115	334
Other localities (bituminous)	†	—	20	161

* Compiled from: Joint Occupation Study, Actuarial Society of America and The Association of Life Insurance Medical Directors, 1929; and Occupation Study, Actuarial Society of America and The Association of Life Insurance Medical Directors, 1938.

† Data not available.

study of tuberculosis in Framingham, Massachusetts (10), it was found that about 1 per cent were suffering from the disease in an active form, and another 1 per cent were classified as having arrested tuberculosis. Physical examination of 100,924 adult white males made by the Life Extension Institute (11) indicated a prevalence rate of about 1½ per cent when suspected cases were included. A somewhat higher percentage, namely 2½ per cent, was found by the Public Health Service (12) from the examination of 10,000 male industrial workers.

Among the anthracite workers examined, the clinical tuberculosis rate was below normal in the younger adult ages, but at ages 35 to 44 clinical pulmonary tuberculosis was diagnosed in about 5 per cent of the hard coal mining

employees; at ages 45 to 54, in 10 per cent; and at ages 55 to 64, in 20 per cent. No such rise with age occurred in any general population group for which comparable data are available.

The prevalence of tuberculosis was greatest among the rock workers. The next to the highest rate occurred among anthracite workers who had changed more than five years previously from very dusty to relatively non-dusty occupations in the industry. The third highest rate was exhibited among persons who had had appreciable exposure to harmful dusts in other industries. Among the regular miners working at the face, the rate was definitely higher than in the control group (men whose dust exposure averaged less than 5 million particles per cubic foot) which showed a prevalence rate of less than 1 per cent.

When the term of service exceeded 20 years, more than 2 or 3 of which involved exposure to heavy concentrations of rock dust, about 37 per cent of such employees [classified as rock workers] showed evidence of pulmonary tuberculosis. Service of 25 to 34 years was associated with a tuberculosis rate of 8 per cent among non-rock workers employed in the haulageways, of 14 per cent among the regular miners, but with a rate under 2 per cent among men exposed to less than 5 million dust particles per cubic foot of air.

Asbestos: Exposure to asbestos dust may produce a pulmonary fibrosis which, like silicosis, may cause disability and death but which does not appear to carry with it a predisposition to tubercle infection and which has a pathology quite distinct from silicosis. The circumstances under which asbestosis will occur are not too clearly defined and undoubtedly there has been a tendency to classify as asbestosis cases in which the causal relationship of asbestos to the condition present has been assumed rather than proved.

Our knowledge of asbestosis is based on individual reported cases. The actual number of fatal cases of asbestosis, supported by postmortem examination, is too few to have any statistical weight but the disease itself and its pathology have been clearly demonstrated. Gardner (13) believes that the action of asbestos dust, unlike silica, may be mechanical and not chemical. If this is so, it would well explain some of the confusing aspects of this disease. The cases described have originated in textile and other asbestos fabricating plants and not in connection with the mining of asbestos. Pedley (14) found that the tuberculosis mortality rate in Thetford Mines (whence 80 per cent of the asbestos used in the United States is derived) did not differ materially from the rate of the Province of Quebec as a whole.

INORGANIC DUSTS OTHER THAN SILICA, ASBESTOS AND COAL DUST

Many industrial dusts contain silica in combined form, as distinguished from free silica, such as combinations with magnesium, iron and aluminum. The effect of silicate dusts upon the lungs, with one exception (asbestos), is problematical. Where exposure to silicate dusts occurs in industrial establishments, under circumstances which might be thought hazardous, one does not see the clinical picture which is presented where free silica is involved nor is there evidence of disability and tendency to infection. Extensive animal experimentation with silicates, both by inhalation and intraperitoneal injection (15), fails to produce any disease akin to silicosis or other evidence of definite disease. It is doubtful whether there is a definite disease to which the term *silicatosis* can be applied, although such a term has been devised. Certainly, the last word has not been said with respect to silicate dusts.

Similarly the dusts of aluminum oxide and some other artificial abrasives, of hematite, and of other inorganic dusts have not been shown to be the cause of marked pulmonary damage. Mortality statistics tend to emphasize the distinction between the effects of dusts containing free silica and other inorganic dusts. This is very strikingly brought out in a study, based on the occupational mortality data of the Registrar-General of England and Wales (5), by Collis and Yule (16). These authors selected for study two groups of occupations—one exposed to silica dust and the other to nonsilica—so chosen that each had as far as possible the same amount of dust exposure, physical effort, exposure to heat or to weather, or any underground environment. Part of the authors' comment on the results as regards respiratory tuberculosis is quoted:

For all ages (20 to 65) the C.M.F.[3] of the Silica Group is no less than 592.2 against 163.5 for the Standard Population, i.e., the mortality is more than three and a half times the normal. For the Non-silica Group, the C.M.F., although actually slightly higher than normal, at first sight hardly seems to differ significantly from the normal; nor would one's judgment be much affected, if instead of making comparison with the Standard Population, one had used the Social Groups III and IV, for which the respective C.M.F.'s are 159.8 and 164.2. But the summary figures conceal interesting changes with age. A glance at the figures shows that in the Silica Group, the ratio of mortality to the normal, though greater than unity even in the lowest age-group,

[3] Comparative Mortality Figure: This figure is defined as the number of deaths that would have occurred in the Standard Population at the rates ruling in the occupation.

rapidly increases as age advances. In the Non-silica Group, the comparative mortality is actually below normal up to age 35; it rises just above normal in the following age-group; but at ages over 45, it is conspicuously above normal.

The report does not give the facts regarding the mortality from respiratory tuberculosis separately for each of the eleven occupations included in either the silica or the nonsilica group. Because of our special

TABLE 3

*Ratio of actual to expected deaths from respiratory tuberculosis among males ages 20 to 65 years, exposed to specified kinds of dusts, England and Wales, 1921–1923**

OCCUPATION	ACTUAL DEATHS	EXPECTED DEATHS	RATIO PER CENT
Silica Dust			
All selected occupations	654	179	365
Tin and copper mine—underground workers, not superintending staff	92	8	1,150
Potters' mill workers; slip makers; potters	105	37	284
Earthenware, china, etc., kiln and oven men, and kiln setters and placers	50	23	217
Metal grinders	221	60	368
Sandstone miners and quarriers	36	17	212
Sandstone masons, cutters, and dressers	150	34	441
Nonsilica Dust			
All selected occupations	162	150.3	108
Brick and plain tile makers, moulders, etc., furnace and crucible pot makers	34	33.7	101
Brick, tile, etc., kiln and oven men	15	22	68
Iron ore mine—underground workers, not superintending staff (Staffordshire and North Riding of Yorkshire)	13	24	54
Limestone miners and quarriers	39	38.6	101
Limestone masons, cutters, and dressers	61	32	191

* Compiled from: Registrar-General's Decennial Supplement, England and Wales, 1921, Part II. Occupational Mortality.

interest in the facts for this particular disease, we have calculated, from the original report of the Registrar-General (5), for each of the selected occupations, the number of deaths from respiratory tuberculosis which might have been expected on the basis of death rates prevailing among all occupied and retired civilian males between the ages of twenty and sixty-five. These results, together with the numbers of deaths which actually occurred, are presented in table 3.

Each of the silica occupations had over twice the average number of

deaths. The extraordinarily high ratio of 1,150 per cent was recorded for tin and copper miners, while sandstone masons, cutters and dressers had a ratio of 441 per cent. On the other hand, only the limestone masons, cutters, and dressers in the nonsilica group exhibited a high ratio, 191 per cent. Why these men should have so high a ratio is not clear. It may be that many of them had carried on their trade, at one time or another, in districts where granite or sandstone were cut and, consequently, had been exposed to silica dust.

So far as the occupations exposed to silica dust are concerned, as we have mentioned, these findings are in agreement with American insurance experience. Unfortunately, there are only a few occupations exposed to inorganic dust, other than those discussed under silica and coal dust, included in the American insurance experience and none of these is entirely free from complicating exposure to silica. In the 1915–1926 Medico-Actuarial Study (6), a small group of grinders of metals had twice the expected number of deaths from tuberculosis, while in a somewhat larger exposure in the period 1925–1936 (7), the number of deaths from tuberculosis was about one and a half times the number expected. In recent years, sandstone grinding wheels have largely been replaced by composition wheels throughout industry. It is a fair assumption, therefore, that most of the grinders were exposed to dust from composition wheels, silicon carbide, aluminum oxide, etc., although undoubtedly some grinders were employed where sandstone wheels are still in use. This comparatively favorable result is at variance with the result for grinders in England and Wales (5) who had a ratio of actual to expected deaths of 368 per cent. That study covered the years 1921 to 1923, and the proportion of workers using sandstone wheels may have been greater than in the later American insurance experience. The report of the Registrar-General brings out the important fact that grinders in the cutlery industry, where the sandstone wheel is much in use, have a much higher mortality than do other grinders. We have determined from the facts presented in this report that among the cutlery grinders there were over seven and a half times as many deaths from respiratory tuberculosis as expected, whereas among other grinders actual deaths were somewhat fewer than three times the expected.

Buffers and polishers of metal, a somewhat similar group, were represented in the 1915–1926 American insurance study (6) by 17,000 life years of exposure. There were 10 deaths from tuberculosis where 7

might have been expected and 18 deaths from influenza and pneumonia where 11 were expected.

In the 1925–1936 study (7) there were 10 deaths from tuberculosis among limestone and marble cutters where one was expected. Here again, as in the case of the British limestone masons, cutters and dressers, the question is raised as to whether some of these men had not worked on granite and other stones as well. Granite and sandstone cutters in the American insurance experience, as we have shown, had more than twenty-six times as many deaths from tuberculosis as expected.

American iron miners apparently have a different type of exposure from the British. We have included them in table 1, somewhat arbitrarily, with the occupations exposed to silica dust. There were 12 deaths from tuberculosis among them where only 1.4 were expected, or a ratio of 857 per cent. This very high ratio suggests that, in some American mines, there may be a greater silica hazard than had been thought. The number of deaths was small, however, and the result cannot be considered conclusive.

METALLIC DUSTS

Hoffman (2), in Bulletin 231, emphasized the danger of exposure to metallic dusts (pages 51–161), but the experience of recent years has not borne out his conclusions. There has not been defined in the various industries in which exposure to metallic dust occurs any definite or specific pulmonary disease resulting therefrom. All the indications are that, where pulmonary disease has been described in conjunction with metallic dust, the blame must be placed on coincidental exposure to silica dust. Macklin and Middleton (17), reporting in 1923, point out that silicosis is associated with the use of natural grindstones and not artificial grindstones and make no mention of ill effects from metal dust. Collis (18) had stated the same general conclusion in his well known Milroy Lecture in 1915 and stated further that the percentage of free silica is the index of harmfulness.

Drinker (19) states that there are no data to indicate that iron in the absence of silica caused pathology in any way comparable to silicosis. Carleton (20) states that hematite is relatively harmless compared with flint and other silica dusts; if inhaled over long periods of time, it might cause fibrosis and tuberculosis but further evidence is needed. Under experimental conditions, it is a relatively harmless dust.

In a series of experiments by Miller and Sayers (15), when iron oxide

dust was injected into the peritoneal cavity of animals, the reaction was inert.

In the process of welding, metals and metallic oxides are volatilized and inhaled into the lungs in a very finely divided state. Reports have been made of roentgen-ray films, taken during the physical examination of welders, which showed an appearance of nodulation resembling fine silicosis. This has given rise to the question as to whether silicosis might be contracted from welding (21, 22), although all these cases were symptom free.

One of the cases reported by Sander came to autopsy following an accidental death. No fibrous tissue was found and it was concluded that the nodular shadows on the film were caused by collections of iron and carbon pigment in the lymph channels of the lung (21, 23).

No satisfactory statistics are available on the mortality of men exposed solely to metallic dust. Perhaps there is as much dust of this character thrown off in grinding as in any other process and the comments regarding the mortality of grinders and of buffers and polishers, given under inorganic dust, are pertinent here. These mixed metal and other dusts from the composition wheels do not seem to have produced mortality rates from tuberculosis comparable in any way with those where the silica hazard is severe.

ORGANIC DUSTS

Until the action of various kinds of dusts upon the lungs was made the subject of experimental studies, the organic dusts, rising from industrial processes, were considered to be responsible for tuberculosis. Knowledge resulting from the extensive studies of silicosis has tended to minimize the possible action of organic dust, both on account of the large average size of the particles and their small numbers when compared with the concentration of inorganic dust particles found in various industries. The presence of pulmonary fibrosis or other structural change caused by organic dust and associated with infection has not been demonstrated among industrial workers. Nor is there evident, in connection with industrial processes involving exposure to organic dust, a clinical picture which could be compared with that associated with silica.

The late Doctor Landis of Philadelphia was one of a group of physicians who were among the first in this country to study tuberculosis among industrial workers. His studies included employees of a number

of textile plants and he stated that there was no evidence of organic dust causing pulmonary diseases (24).

The mortality picture as regards organic dust and tuberculosis is confused. In the Registrar-General's Report (5), out of thirteen classes of textile workers, six had above average death rates from tuberculosis but in only one class—wool, worsted, card, comb or frame (not spinning frame) tenters—was the rate as much as 59 per cent above average. No

TABLE 4

*Standardized mortality (comparative mortality figures) from respiratory tuberculosis of males ages 20 to 65 years in occupations exposed to organic dust compared with that of all occupied and retired civilian males taken as 1,000, England and Wales, 1921–1923**

OCCUPATION	MORTALITY RATIO
All occupied and retired civilian males	1,000
Wool sorters	1,065
Cotton blow room operatives—skilled	750
Rag grinders, wool willowers, etc.	1,093
Cotton card and frame (not spinning frame) tenters	1,057
Wool, worsted card, comb, or frame (not spinning frame) tenters	1,591
Cotton strippers and grinders and card room jobbers	796
Cotton spinners and piecers	1,072
Wool and worsted spinners and piecers	898
Cotton—doublers, winders, warpers, beamers, etc.	869
Wool and worsted—doublers, winders, warpers, beamers, etc.	510
Cotton weavers	731
Woolen and worsted weavers	1,162
Weavers of other textiles	904
Boot and shoe clickers and cutters	1,820
Skilled boot and shoe operatives, not clickers or cutters	1,821
Bakers and pastry cooks	1,016
Tobacco factory operatives	2,002
Upholsterers, coach trimmers, and bedding makers	1,262
Drafters and brush makers	2,376

* Compiled from Registrar-General's Decennial Supplement, England and Wales, 1921, Part II. Occupational Mortality.

other class showed more than 16 per cent excess, while in several classes the rate was quite low. On the other hand, boot and shoe factory workers showed an 82 per cent excess; tobacco factory operatives had 100 per cent excess mortality, and brush makers and drafters, 138 per cent excess. The rate for upholsterers, coach trimmers, bedding makers was 26 per cent above the average. Table 4 gives the Standardized Mortality for the principal occupations exposed to organic dust.

In the American insurance experience, covering the years 1915–1926 (6), also, the ratio of actual to expected deaths was above average for several occupational groups exposed to organic dust. The ratios of actual to expected deaths for the more important of these were: cotton mill operatives, 176 per cent; woolen mill operatives, 134 per cent; upholsterers, 225 per cent; cigar makers and tobacco factory operatives, 174 per cent.

The occupations discussed here have been traditionally classified among the dusty trades. One may well question, however, the inclusion in such a list of boot and shoe and of tobacco factory workers. The great bulk of workers in these industries cannot be said to be exposed to appreciable quantities of dust. But taking the list as it stands, there is obviously no resemblance between the tuberculosis ratios for these occupations and the very high ratios for occupations with exposure to silica dust. Some condition connected with the work of persons in these trades obviously is associated with the above-average incidence of tuberculosis. It may be that the less robust workers are attracted to them. Whatever may be the explanation, clinical findings would suggest that dust is not an important factor in the high incidence of tuberculosis in these trades.

FUNGUS DISEASES OF THE LUNGS

Dust may convey to the respiratory tract various types of fungi. Some of these apparently have no clinical significance. Others are pathogenic and may produce either acute or chronic disease. The constantly increasing use of the roentgen-ray in diagnosis and in routine physical examinations has served to awaken interest in fungoid diseases about which too little is known and which are not uncommonly diagnosed as tuberculosis (25). Our knowledge of the subject is very incomplete but it is recognized that these fungus diseases are frequently occupational in origin and associated with dust inhalation and may result fatally. Mortality statistics are entirely lacking, but the reports of Fawcitt (26) and the recent studies of coccidioidal infection in California (27) indicate that such pulmonary diseases may be quite important.

PNEUMONIA

The effect of dust inhalation upon the incidence of and mortality from pneumonia has been the subject of much study without any clear-cut picture of the rôle of dust resulting (32, 33). The foundry industry has

an unusually high mortality from pneumonia (28) and the same is true of certain occupations in the steel industry (29, 30). Exposure to dust is associated with some of these occupations and usually extremes of temperature are also encountered with such other conditions as would tend to cause dampness and chilling. So far as silica is concerned, a high mortality from pneumonia is associated with the silica trades, both in this country and abroad. Whether silica acts as a predisposing cause of pneumonia or due to the accompanying lung damage the prognosis is more unfavorable, cannot be shown from the figures available.

For some years, a series of interesting studies has been carried on in Pittsburgh by Haythorn and Meller and their associates in an endeavor to establish any possible connection between the prevailing high mortality rate from pneumonia in that city and atmospheric pollution. These reports are interesting and suggestive but not entirely conclusive. The following quotation is from a recently published report of these authors (31).

> It is further seen . . . that during the years from 1932 to 1935 when the depression was at its height, when air pollution from industrial flues was greatly decreased and when economic and living conditions were at their worst, there was a great decrease in the number of deaths from pneumonia. However, the decrease occurred in females as well as males so that the change cannot be attributed to conditions within the plants, such as overheating and rapid chilling of the employees.

SUMMARY

Early occupational mortality studies focussed attention on the importance of dust as a cause of respiratory diseases. Virtually all kinds of dusts were implicated. Present day clinical and laboratory studies point to the serious damage to the lung tissue caused by a few dusts, notably silica and asbestos, and to the relatively little damage to the lung tissue caused by many other dusts. The most complete recent mortality studies have been examined in the light of this clinical and laboratory knowledge. These mortality data, while yielding highly suggestive information, are very incomplete and permit only qualified general conclusions regarding the effects of dust exposure on the incidence of respiratory diseases for even the broad classes of dust with one exception—silica dust. The death rates from tuberculosis among men in occupations in which there is exposure to free silica so

far exceed those found for men in other pursuits, as to leave little room for doubt that silica is implicated.

With regard to silicate and other inorganic dusts not containing free silica, American mortality data are very meagre. The relatively low death rate from tuberculosis among grinders in the small American insurance experience suggests that the effects of aluminum oxide, silicon carbide and other substances used in manufactured wheels are slight. British data, much more complete, show lower than average tuberculosis mortality up to age thirty-five, but substantially higher mortality after age forty-five for a group of men exposed to inorganic dusts other than silica dust. Whether this unfavorable situation later in life is due to the cummulative effect of such dusts with duration of exposure or whether it is due to the inclusion in these occupational groups of a substantial number of men who had been exposed also to silica dust, is not clear.

There are no mortality data for men exposed solely to metallic dusts.

Recent statistical studies, like the earlier ones, show higher than average death rates from tuberculosis among men employed in certain occupations or industries in which organic dust is generated. In no instance, however, does the rate for a group of this kind approach in magnitude the extremely high rates found among men employed in some of the occupations in which there is exposure to silica dust, nor, in the light of clinical knowedge, is it possible to account for the excess mortality on the score of damage to the lung tissue caused by dust.

The relationship between dust inhalation and acute pulmonary disease remains a field for further investigation. A splendid contribution to our knowledge of this subject has already been made by the United States Public Health Service in their bulletins on *The Health of Workers in Dusty Trades* (32, 33). A greater volume of data of this kind and more detailed studies of occupational mortality are vitally needed to guide the work of industrial physicians and hygienists in this field.

REFERENCES

(1) HOFFMAN, F. L.: The mortality from consumption in the dusty trades, Bull. 79, U. S. Bur. Lab., November, 1908.

(2) HOFFMAN, F. L.: The mortality from respiratory diseases in the dusty trades, Bull. 231, U. S. Bur. Lab. Stat., 1918.

(3) HOFFMAN, F. L., Chairman: Preliminary report of Committee on Mortality from Tuberculosis in Dusty Trades, Working Conditions Service, U. S. Dept. Lab., 1919.

Second preliminary report of Committee on Mortality from Tuberculosis in Dusty Trades, Natl. Tuberc. Assn., 1919.

(4) WHITNEY, JESSAMINE S.: Death rates by occupation, Natl. Tuberc. Assn., June, 1934.
(5) Registrar-General's Decennial Supplement: England and Wales 1921, Part II, Occupational mortality, H. M. Stat. Off., London, 1927.
(6) Joint Occupation Study, Actuarial Society of America and The Association of Life Insurance Medical Directors, 1929.
(7) Occupation Study, Actuarial Society of America and The Association of Life Insurance Medical Directors, 1938.
(8) SAYERS, R. R., Chairman: Report of the Committee on the Prevention of Silicosis through Medical Control, U. S. Dept. Lab., November, 1936.
(9) SAYERS, R. R., BLOOMFIELD, J. J., DALLAVALLE, J. M., JONES, R. R., DREESSEN, W. C., BRUNDAGE, D. K., AND BRITTEN, R. H.: Anthraco-silicosis among hard coal miners, Pub. Health Bull. 221, U. S. Pub. Health Service, 1936, p. 85.
(10) National Tuberculosis Association: Framingham community health and tuberculosis demonstration, Framingham Monograph No. 10, July, 1924, p. 69.
(11) SYDENSTRICKER, E., AND BRITTEN, R. H.: The physical impairments of adult life, Am. J. Hyg., 1930, *11*, 89, 100.
(12) BRITTEN, R. H., AND THOMPSON, L. R.: A health study of ten thousand male industrial workers, Pub. Health Bull. 162, 1926, p. 161.
(13) GARDNER, L. U.: Reaction of the living body to different types of mineral dusts with and without complicating infection, Tech. Pub. No. 929, Am. Inst. Min. & Met. Eng., May, 1938.
(14) PEDLEY, F. G.: Asbestosis, Canad. J. Pub. Health, November, 1930.
(15) MILLER, J. W., AND SAYERS, R. R.: The physiological responses of the peritoneal tissue to dusts introduced as foreign bodies, Pub. Health Repts. 49, January 19, 1934.
(16) COLLIS, E. L., AND YULE, G. U.: The mortality experience of an occupational group exposed to silica dust, compared with that of the general population and an occupational group exposed to dust not containing silica, J. Indust. Hyg., 1933, *15*, 395.
(17) MACKLIN, E. L., AND MIDDLETON, E. L.: Report on the grinding of metals and cleaning of castings with special reference to the effects of dust inhalation upon the workers, U. K. Home Off., H. M. Stat. Off., 1923.
(18) COLLIS, E. L.: Industrial pneumoconiosis with special reference to dust phthisis, Milroy Lectures, 1915; reprinted by H. M. Stat. Off., 1919.
(19) DRINKER, P.: Causation of pneumoconiosis, Harvard School of Public Health, 1937.
(20) CARLETON, H. M.: The effects produced by the inhalation of hematite and iron dusts in guinea pigs, J. Hyg., 1927, *26*, 227.
(21) Health protection in welding, Industrial Health Section, Metropolitan Life Insurance Co., (b) 513 L.W.
(22) DOIG, A. T., AND MCLAUGHLIN, A. I. G.: X-ray appearances of the lungs of electric arc welders, Lancet, London, 1936, *230*, 771.
(23) ENZER, N., AND SANDER, O. A.: Chronic lung changes in electric arc welders, J. Indust. Hyg. & Toxicol., 1938, *20*, 337.
(24) LANDIS, H. R. M.: The relation of organic dust to pneumokoniosis, J. Indust. Hyg., 1925, *7*, 1.
(25) SAYERS, R. R., AND MERIWETHER, F. V.: Miliary calcifications of the lungs due to unknown cause, Reprint 1431 from Pub. Health Repts. 45, December, 1930.
(26) FAWCITT, R.: Fungoid conditions of the lung, Part I, Brit. J. Radiol., New Series No. 99, March, 1936; Part II, Brit. J. Radiol., New Series No. 102, June, 1936.
(27) DICKSON, E. C.: Coccidioides infection, Arch. Int. Med., 1937, *50*, 1029.

(28) Iron foundry workers show highest percentage of deaths from pneumonia, Statistical Bulletin, Metropolitan Life Insurance Co., March, 1928, *9*, 3.

(29) BLOOMFIELD, J. J.: Engineering aspects of industrial epidemiology, Indust. Med., 1938, *7*, 7.

(30) KIBBEY, C. H.: Pneumonia and tuberculosis among industrial workers, Am. J. Pub. Health, 1937, *27*, 6.

(31) HAYTHORN, S. R., AND MELLER, H. B.: Pneumonia, Ibid., 1938, *28*, 483.

(32) THOMPSON, L. R., BRUNDAGE, D. K., RUSSELL, A. E., AND BLOOMFIELD, J. J.: The health of workers in dusty trades. I. Health of workers in a Portland Cement Plant, Pub. Health Bull. 176, U. S. Pub. Health Service, April, 1928.

(33) RUSSELL, A. E., BRITTEN, R. H., THOMPSON, L. R., AND BLOOMFIELD, J. J.: The health of workers in dusty trades. II. Exposure to siliceous dust (granite industry), Pub. Health Bull. 187, U. S. Pub. Health Service, July, 1929.

TUBERCULOUS LESIONS IN MALE INDUSTRIAL WORKERS[1,2]

Their Incidence and Significance as Disclosed by Stereoscopic Chest Roentgenograms

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Mortality records (1) compiled over two centuries ago in the city of London at the advent of the industrial revolution disclosed the inception of a virtual tuberculosis epidemic which persisted for a hundred years and witnessed a death-rate rise to 700 per 100,000 annually. Even before this period certain early writers, among whom may be mentioned Agricola (2), Paracelsus (3), and Ramazzini (4), had commented on the excessive occurrence of pulmonary disease in miners and other workmen exposed to pernicious dusts. It became increasingly apparent from these observations and the hundreds of others which followed that phthisis was exacting a frightful toll from many industrial workers, particularly those engaged in the dusty trades, and eventually the conviction grew that all industry and tuberculosis were linked as malevolent companions. Doubtless this tenet was fully merited since the early factories and industrial communities offered new and intimate contact with the tubercle bacillus to workmen pitifully crowded under unhygienic surroundings. The adoption of machine tools also served to intensify the hazard from tuberculosis in the occupations offering exposure to harmful dust.

Since Koch's discovery of the tubercle bacillus in 1882, there has been a notable improvement in industrial hygiene throughout the civilized world, particularly in the United States during the past quarter century. Dublin and Lotka (5) have noted recently that the tuberculosis mortality rate among industrial policy holders of the Metropolitan Life Insurance Company is only slightly greater and is declining more rapidly than that for the general population of the United States Death Registration

[1] Read as part of the Symposium on *Tuberculosis in Industry* at the joint session of the Pathological, Clinical, Social Work and Administrative Sections at the 34th annual meeting of the National Tuberculosis Association, Los Angeles, California, June 23, 1938.

[2] From the Field Division of The Saranac Laboratory for the Study of Tuberculosis of the Edward L. Trudeau Foundation, Saranac Lake, New York.

Area. Unfortunately there are no comprehensive analyses of tuberculosis mortality rates by occupation available in this country, but Lanza and Vane (6) have estimated the prevalence of silicosis in various occupations and have indicated the influence which this factor exerts in increasing the number of deaths from respiratory tuberculosis. From these studies it appears reasonable to assume that the elimination of the excess number of deaths from pulmonary tuberculosis among workers in occupations involving a dust hazard would result in so improving the mortality rate from this cause among all industrial workers that their rate would be equal to or even less than that for the general population.

A clear distinction should be made between the pulmonary tuberculosis which occurs in industry as it does to a greater or less extent in all walks of life, and *industrial tuberculosis* which is a disease directly attributable to the industrial environment and eligible as such to compensation under occupational disease legislation. Until complete and accurate mortality rates are determined for the principal occupations there does not appear to be ample justification for considering pulmonary tuberculosis an occupational disease except in the presence of a well established and definitely recognized predisoposing condition such as silicosis. It should also be emphasized that nonoccupational pulmonary tuberculous lesions may and do occur among the workmen in every industry including those employed in the hazardous trades. In order to illustrate the difference between tuberculosis in industry and industrial tuberculosis this paper will contrast the incidence and significance of tuberculous lesions discovered in two groups of workmen—one engaged in a large industry with no important tuberculosis hazard, and the other employed in an occupation offering exposure to silica.

The first group is comprised of 5,000 steel mill workers whose mortality from tuberculosis of the respiratory system is well below that for all occupations, according to Dublin and Vane (7) who placed them fifty-third in a list of seventy-two occupations arranged in the order of the number of deaths from this disease. The second group consists of 5,000 men who are engaged in mining where they are exposed in various degrees to the inhalation of fine silica dust and other relatively inert substances. Underground miners head the list of the seventy-two occupations which Dublin and Vane classified according to tuberculosis mortality experience.

Serial stereoscopic chest roentgenograms, which provide the most reliable method for determining the prevalence of significant pulmonary

tuberculous lesions, were employed in these studies representing part of the investigations conducted by the Field Division of the Saranac Laboratory from 1933 to 1938. During this five year period medical departments in various industries under our supervision prepared excellent films of approximately 25,000 workmen. These were interpreted at the Trudeau X-ray Laboratory under the direction of Dr. Homer L. Sampson. Any observed indication of pulmonary abnormality was noted and each pair of roentgenograms was classified according to the degree of reaction to inhaled dusts as described (8) in United States Public Health Service Reprint No. 1696. Pulmonary lesions designated as tuberculous included only those generally accepted as characteristic of the reinfection type. Evidence of primary tuberculosis, pleurisy, or changes which might have resulted from nontuberculous infections or other pathological processes failed to qualify for inclusion in this group.

The results obtained in the roentgenological examination of large groups have been reviewed recently by Kayser-Petersen (9) and by Bloch, Francis, Eisele and Mason (10). The incidence of tuberculous lesions discovered by this procedure varies considerably, depending upon the factors which influence tuberculosis morbidity, the quality of the roentgenogram, and the competence of the interpreter. A preliminary analysis of our data disclosed that of 4,012 white male workmen who were found to have no discernible evidence of reaction to occupational exposure, and who were employed in various industries located in several sections of the United States, there were 191 with tuberculous lesions, a crude incidence of 4.76 per cent. However, crude rates for the incidence of tuberculous lesions are of little value unless accompanied by an analysis of the age distribution of the group studied since this factor exerts a marked influence on the number of lesions which will be encountered, as Fellows (11) has clearly demonstrated.

STEEL MILL WORKERS

Among the large industrial groups included in our studies, steel mill workers were observed to have an age distribution and incidence of tuberculous lesions most nearly comparable with that determined for normal workmen from other industries. The second series of 5,000 men (including both applicants for employment and regular employees) who appeared for an original examination at a single steel plant clinic were

TABLE 1

Incidence of pulmonary lesions interpreted as tuberculous in routine stereoscopic chest roentgenograms of male employees and applicants for employment in a midwestern steel plant by race and age group, 1937

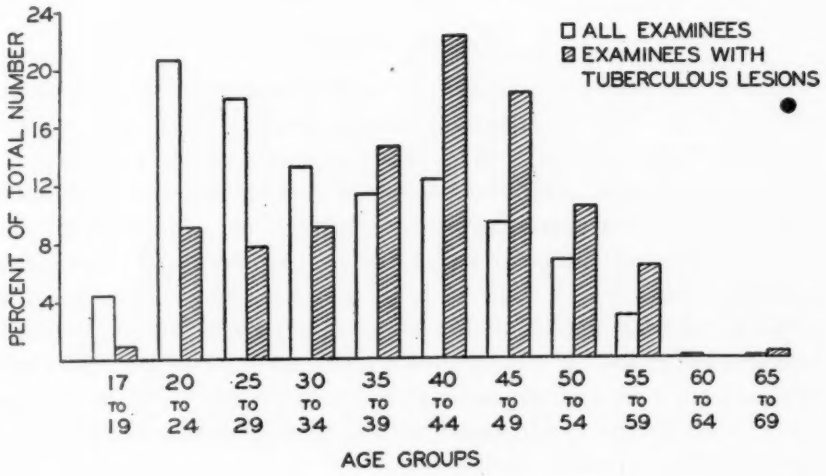
AGE GROUP	WHITE MALES			MEXICAN MALES			NEGRO MALES			TOTAL MALES		
	Total number	Number with lesions	Rate per 100	Total number	Number with lesions	Rate per 100	Total number	Number with lesions	Rate per 100	Total number	Number with lesions	Rate per 100
17–19	187			3			3			193		
		2	1.07		0	—		1	—		3	1.55
20–24	866			37			25			928		
		20	2.31		1	2.70		1	4.00		22	2.37
25–29	752			83			30			865		
		17	2.26		4	4.82		0	—		21	2.43
30–34	556			166			63			785		
		20	3.60		6	3.61		2	3.17		28	3.57
35–39	476			159			61			696		
		32	6.72		9	5.66		2	3.28		43	6.18
40–44	519			63			39			621		
		49	9.44		7	11.11		6	15.38		62	9.98
45–49	395			41			21			457		
		40	10.13		3	7.32		0	—		43	9.41
50–54	287			9			10			306		
		23	8.01		0	—		1	10.00		24	7.84
55–59	123			4			5			132		
		14	11.38		1	25.00		0	—		15	11.36
60–64	7						2			9		
		0	—					0	—		0	—
65–69	7									7		
		1	14.29								1	14.29
70–74	1									1		
		0	—								0	—
Totals	4,176			565			259			5,000		
		218	5.22		31	5.49		13	5.02		262	5.24

CHART I

INCIDENCE OF TUBERCULOUS LESIONS OBSERVED IN ROUTINE STEREOSCOPIC CHEST ROENTGENOGRAMS OF WHITE MALE STEEL MILL WORKERS BY AGE GROUPS-1937

CHART II

PERCENTAGE DISTRIBUTION BY AGE GROUPS OF ALL WHITE EXAMINEES AND OF ALL THOSE WITH TUBERCULOUS LESIONS - STEEL MILL WORKERS-1937



therefore chosen for detailed study. A few men (less than 1.0 per cent of all those examined) were excluded from the analysis because of the presence of silicosis. Of the 5,000 males, 4,176 (83.52 per cent) were white; 565 (11.30 per cent) were Mexican; 259 (5.18 per cent) were Negroes. Those with tuberculous lesions constituted 5.22 per cent of the white males, 5.49 per cent of the Mexican males, and 5.02 per cent of the Negro males. The crude incidence rate for the entire group was 5.24 per cent.

The distribution of tuberculous lesions among the 5,000 steel mill workers is shown by age groups in table 1 and is represented graphically for the 4,176 white steel mill workers in chart I. The incidence of lesions increases with advancing age, rising from about 1.0 per cent for those less than twenty years of age to 12.5 per cent for those from sixty-five to seventy-four years of age.

Chart II illustrates graphically the distribution of the 4,176 white steel mill workers among the principal age groups and also shows the proportion of the 218 white workers with tuberculous lesions discovered in each of the same age groups. The age group from twenty to twenty-four includes the largest proportion of steel mill workers while the number of workmen in each succeeding age group decreases quite regularly until sixty, after which age few men are employed. Despite the fact that the preponderance of all the white steel mill workers are young men, the greatest number of persons with tuberculous lesions is found in the group from forty to forty-five years of age, and 55.5 per cent of all the men with lesions are from thirty-five to forty-nine years of age.

WHITE MINERS

Among the workmen engaged in various industries which have been studied in our field investigations, a large group of white miners proved to be of considerable interest. Though the occupation is described as mining, it should be pointed out that this group includes not only underground miners but also office workers, mechanics, surface laborers and representatives of the great variety of occupations required to operate a mining property. A series of 5,000 men (including both regular employees and a few applicants for employment) appearing for an original examination at any of several clinics which served a district devoted to the extraction of a single mineral were chosen for study in the same proportions as they contributed to the total of approximately 10,000 men examined at those clinics.

TABLE 2

Incidence of pulmonary lesions interpreted as tuberculous in routine stereoscopic chest roentgenograms of miners by degree of reaction to dust exposure and age groups, 1937

AGE GROUP	NORMAL		P_1		P_2		S_1		S_2		S_3		TOTALS	
	Total number	With lesions	Total number	With lesions	Total number	With lesions	Total number	With lesions	Total number	With lesions	Total number	With lesions	Total number	With lesions
17–19	69		1										70	
		3												3
20–24	382		24		2								408	
		16		1										17
25–29	420		128		14		1						563	
		15		2		2								19
30–34	277		184		25		15						501	
		14		14		2		5						35
35–39	206		204		65		39		8				522	
		13		10		5		12		4				44
40–44	169		269		122		94		19		1		674	
		11		12		19		19		6		1		68
45–49	146		251		169		181		44		3		794	
		10		17		19		43		21		2		112
50–54	100		206		141		192		52		5		696	
		6		19		24		46		30		3		128
55–59	52		104		63		135		61		1		416	
		6		16		6		39		32				99
60–64	24		42		32		83		43		4		228	
		4		7		9		21		18		3		62
65–69	7		22		9		30		18				86	
		1		3		4		7		8				23
70–74	7		11		6		7		7				38	
		1		4				3		2				10
75 and over			3				1						4	
Totals	1,859		1,449		648		778		252		14		5,000	
		100		105		90		195		121		9		620

CHART III

INCIDENCE OF TUBERCULOUS LESIONS OBSERVED IN ROUTINE STEREOSCOPIC CHEST ROENTGENOGRAMS OF WHITE MALE MINERS BY AGE GROUPS FOR VARIOUS DEGREES OF REACTION TO DUST EXPOSURE-1937

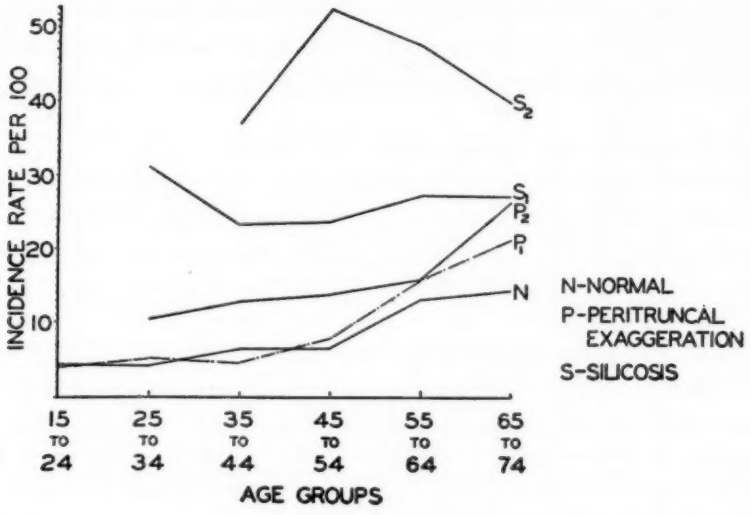
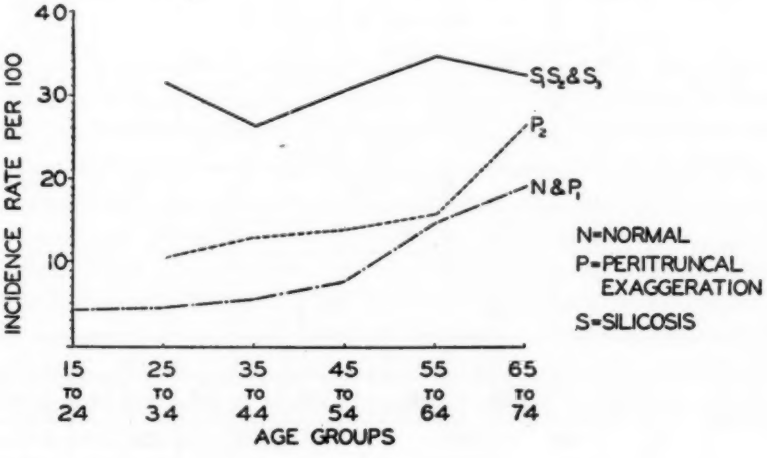


CHART IV

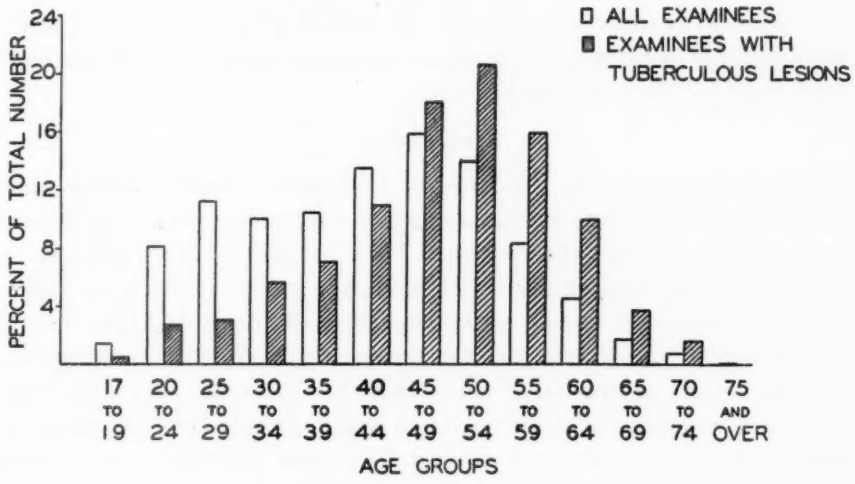
INCIDENCE OF TUBERCULOUS LESIONS OBSERVED IN ROUTINE STEREOSCOPIC CHEST ROENTGENOGRAMS OF WHITE MALE MINERS BY AGE GROUPS FOR VARIOUS DEGREES OF REACTION TO DUST EXPOSURE-1937



The roentgenograms of these 5,000 miners were classified (8) into six groups according to their exhibited degree of reaction to dust exposure. Briefly stated, the classifications designate: (*1*) the normal, N; (*2*) the first definite evidence of nonspecific reaction to dust, described as first degree peritruncal exaggeration or P_1; (*3*) marked evidence of nonspecific reaction to dust, described as second degree peritruncal exaggeration or P_2; (*4*) the first definite evidence of specific reaction to dust (early silicosis), described as first degree nodulation or S_1; (*5*) marked evidence of specific reaction to dust (advanced silicosis), described as second degree

CHART V

PERCENTAGE DISTRIBUTION BY AGE GROUPS OF ALL EXAMINEES AND OF ALL THOSE WITH TUBERCULOUS LESIONS- WHITE MINERS 1937



nodulation or S_2; and (*6*) extensive evidence of specific reaction to dust (massive silicosis), described as third degree nodulation or S_3.

The distribution of tuberculous lesions among the 5,000 white miners is shown by age groups and by degree of reaction to dust in table 2, and is represented graphically in charts III and IV. The incidence of tuberculous lesions increases as the degree of reaction to dust progresses. Those with tuberculous lesions constitute 5.38 per cent of the group classified as normal, 7.25 per cent of the P_1's, 13.89 per cent of the P_2's, 25.07 per cent of the S_1's, 48.02 per cent of the S_2's, and 64.29 per cent of the S_3's. The crude incidence rate for the entire group is 12.40 per

cent. Incidence rises with advancing age for the groups whose roentgenograms show no evidence of specific reaction to dust, but, in the presence of silicosis, the incidence is so high that it overshadows the influence of age.

Chart V illustrates graphically the distribution of the 5,000 miners among the principal age groups, and also represents the proportion of the 620 men with tuberculous lesions discovered in each of the same age groups. The largest number of miners is found in the age group from forty-five to forty-nine, while the greatest number of persons with tuberculous lesions are in the age group from fifty to fifty-four. Approximately 55 per cent of all the men with lesions are from forty-five to fifty-nine years of age.

A comparison of chart II with chart V reveals the marked difference in the age distribution of the two occupational groups and also indicates that men with tuberculous lesions are found preponderantly at fairly advanced age periods, the maximum for miners being reached ten years later than for the steel mill workers.

DISCUSSION

As age advances, the incidence of tuberculous lesions among white male industrial workers increases steadily. What reasons may be offered in explanation of this observation? Do tuberculous lesions continue to make their first appearance in all adult age groups or does the higher incidence observed among older workmen simply reflect the greater prevalence of the disease among the young adults of former years? Is tuberculosis contracted in early adult life to become manifest years later as a reactivation of a long latent lesion, or is it newly acquired by older men as suggested by their tuberculosis mortality rates which mount steadily with advancing age?

If tuberculous lesions are nearly all acquired in youth, it would appear unnecessary to continue the costly reëxamination of workmen whose roentgenograms remain negative after the critical age period. On the other hand if new lesions are acquired at all ages it would seem particularly desirable to examine the older age groups since their morbidity and mortality from pulmonary tuberculosis are known to be high.

Table 3 shows the apparent increase in the incidence of tuberculous lesions occurring each year among 1,000 white male steel mill workers at different age periods. These data indicate that an average of only 2.3 new cases each year among 1,000 workers accounts for the rise in

incidence previously described. Fellows and Ordway (12) have noted that new cases of tuberculous lesions appear among previously negative white office workers at rates which have decreased from 7 per 1,000 in 1928 to 2 per 1,000 in 1936. These figures are in accord with our own unpublished observations and strengthen the opinion that the rise in incidence of tuberculous lesions with advancing age is due to the development of new cases at all ages. Table 3 also suggests that new lesions apparently develop with about equal facility at any age. Though one of the age groups shows a decided increase over the average rate, it is doubtful if any significance should be attached to this deviation which would probably disappear if larger groups were studied.

TABLE 3

Apparent increase in the incidence of tuberculous lesions among white male steel mill workers per 1,000 per year, 1937

AGE GROUP	OBSERVED INCIDENCE OF LESIONS PER 1,000	APPARENT INCREASE IN INCIDENCE PER 1,000 OVER PREVIOUS AGE GROUP	APPARENT INCREASE* IN INCIDENCE PER YEAR PER 1,000
15–24	21		
25–34	28	7	.7
35–44	81	53	5.3†
45–54	92	11	1.1
55–64	108	16	1.5
65–74	125	17	1.7
Overall	52	—	2.3

* These figures would be increased very slightly if the incidence of lesions among those dying of all causes was greater than that among those remaining alive.

† Fellows's (11) data show no excessive incidence for this age group. His value can be calculated as 2.2 for white male office workers, 1933.

Table 4 compares the incidence of tuberculous lesions among white male steel mill workers with the mortality from tuberculosis of the respiratory system among a large group of white male industrial workers by age groups for 1937. The resultant ratio indicates that one death occurs for each eighty cases with recognizable lesions. It is noteworthy that this ratio is quite constant for most adult age groups, suggesting that white males between the ages of twenty and sixty-five appear to offer much the same degree of resistance to tuberculous infection.

Since this ratio of incidence to mortality appears to maintain a fairly constant level for most adult age groups at the present, it is interesting to determine whether or not this same level existed ten years ago for each

of the age groups which were then in the next preceding group. The demonstration of a constant or slightly increasing ratio of incidence to mortality would support the opinion that the greater incidence of tuberculous lesions among older workmen is merely the reflection of a greater prevalence existing in the past. Table 5 makes a comparison of this nature and shows that the level of the ratio of incidence to mortality was generally lower ten years ago than it is to-day. This finding fails to reveal the higher rates of incidence in any age group necessary to account for the lesions observable to-day in the succeeding age group.

If ratios of probable incidence to mortality are calculated for white male steel mill workers in 1927 they are found to be fairly constant for most age groups but at a lower level than at the present time. These

TABLE 4

A comparison of the incidence of tuberculous lesions among white male steel mill workers with the mortality from tuberculosis of the respiratory system among white male industrial workers by age groups for 1937

AGE GROUP	MORTALITY* PER 100,000 (1937)	INCIDENCE PER 100,000 (1937)	INCIDENCE / MORTALITY
20–24	30.7	2,310	75
25–34	59.4	2,830	48†
35–44	96.0	8,140	85
45–54	119.1	9,240	78
55–64	135.5	10,780	80

* Provisional death rates from tuberculosis of the respiratory system among white male industrial policy holders of the Metropolitan Life Insurance Company, 1937.

† The incidence data for this age group show an unexpected deviation which might disappear if larger groups were studied.

workers therefore seem less likely to die of a recognizable tuberculous lesion to-day than ten years ago. Since Drolet (13) has shown that the number of reported cases for each death from pulmonary tuberculosis has not changed appreciably over the last twenty years, it would appear that the constantly improving tuberculosis mortality experience among industrial workers can be explained by the fact that fewer men than formerly develop clinical disease from their recognizable lesions. This may indicate either an improvement in the inherent immunity of white males or the favorable influence exerted by better hygiene and improved standards of living.

The incidence of recognizable tuberculous lesions was not as high among Negro male steel mill workers as among the white males. Though

the number of Negroes was not large enough to provide an accurate analysis of incidence by age, it is apparent from an inspection of table 1 that their data are very similar to those for white males as previously observed by Lindberg (14). This observation is interesting when it is recalled that the tuberculosis mortality rates for Negro males exceed those for white males in the manner shown by chart VI. The incidence of lesions among Mexican males was only slightly greater than that among

TABLE 5

A comparison of the incidence of tuberculous lesions observed in various age groups of white male steel mill workers for 1937 with the calculated incidence for the same age groups ten years earlier

AGE GROUP	OBSERVED INCIDENCE PER 1,000 IN THE SUCCEEDING TEN-YEAR AGE GROUP 1937*	OBSERVED INCIDENCE PER 1,000 IN 1937 REVISED†	CALCULATED INCIDENCE PER 1,000 1927‡	TEN YEARS AGO THE RATIO OF $\frac{\text{INCIDENCE}}{\text{MORTALITY}}$ IN THIS AGE GROUP WAS:
15–24	28	34	61	Lower
25–34	81	92	57	Higher§
35–44	92	106	135	Lower
45–54	108	123	141	Lower
55–64	125	137	132	Much the same

* This assumes that no cases of new lesions have appeared in ten years and that the incidence of tuberculous pulmonary lesions among those dying from all causes in each age group is the same as that discovered in those who are living in that age group.

† The observed incidence has been revised to allow for the average number of deaths from pulmonary tuberculosis occurring in each age group over a ten-year period. This now assumes that the incidence of tuberculous pulmonary lesions among those dying from all causes other than pulmonary tuberculosis in each age group is the same as that among those living in the same age group.

‡ Calculated by assuming that $\frac{\text{Incidence}}{\text{Mortality}}\ (1927) = \frac{\text{Incidence}}{\text{Mortality}}\ (1937)$.

§ See footnote, table 3. The incidence data for this age group show an unexpected deviation which might disappear if larger groups were studied. It is more reasonable to assume that the data deviate from the average than to attach any special significance to this particular age group.

white males despite the former's excessive mortality rates. Lack of the inherent immunity (15) which characterizes white races may partially explain the higher death rates among both the Negro and Mexican males with tuberculous lesions.

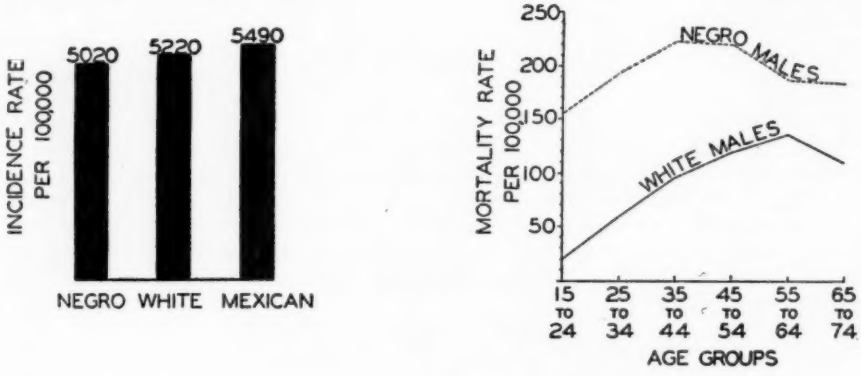
Among the white miners exposed in various degrees to the inhalation of harmful silica dust, the incidence of pulmonary tuberculous lesions increases as the degree of reaction to dust progresses. Since silicosis is

a condition which ordinarily develops slowly it is important to ascertain whether or not this rise in incidence can be accounted for by advancing age inasmuch as that factor exerts such a marked influence on the rates for workmen with no specific dust reaction. Chart III illustrates the incidence of tuberculous lesions among white miners with various degrees of reaction to dust, by age groups. An inspection of this chart leaves little room for doubt that evidence of reaction to silica dust is associated with a greatly increased prevalence of tuberculous lesions.

Miners in the classification which represents the earliest recognizable reaction to dust (first degree peritruncal exaggeration) have an incidence

CHART VI

A COMPARISON OF THE RATES OF INCIDENCE OF TUBERCULOUS LESIONS AMONG NEGRO AND WHITE MALE STEEL MILL WORKERS WITH THE MORTALITY RATES° FROM TUBERCULOSIS OF THE RESPIRATORY SYSTEM AMONG NEGRO AND WHITE MALE INDUSTRIAL POLICY HOLDERS OF THE METROPOLITAN LIFE INSURANCE COMPANY – 1937 °PROVISIONAL



of tuberculous lesions comparable with those in the group designated as normal. The two groups have therefore been combined in chart IV. In order to permit a comparison of the incidence of tuberculous lesions among silicotics and nonsilicotics, the three stages of silicosis have also been grouped in chart IV.

The incidence of tuberculous lesions in the group of normal miners shows the same tendency to increase with age as has been noted in steel mill workers, but the prevalence of lesions among miners less than thirty-five years of age is nearly twice as great as among steel mill workers of the same age. Doubtless the generally higher level of tuberculous in-

fection in the mining community is partially responsible for this finding. After miners have developed a definite dust reaction, not sufficiently advanced to designate as silicosis, their susceptibility to tuberculosis is increased considerably at all age periods, as may be observed in chart IV by comparing the incidence of lesions in the group with marked peritruncal exaggeration (P_2) and in the normal miners of the same age. Age continues to influence the incidence of tuberculous lesions among miners until they become silicotic, whereupon its effect is completely outweighed.

In this group of white miners the incidence of tuberculous lesions increases with the degree of the silicosis, tuberculous lesions being found in approximately one-quarter of the group with first stage silicosis, one-half of those in the second stage, and 65 per cent of those in the third stage. Chart IV demonstrates that if normal miners of twenty-five to thirty-four develop silicosis their chance of having a recognizable tuberculous lesion is increased by more than seven times, while among miners of sixty-five to seventy-four the chance of this occurrence is merely doubled. Hence it may be said that tuberculosis with silicosis is an occupational disease seven out of eight times in miners less than thirty-five years of age, but only once every other time in miners more than sixty-five years old.

SUMMARY

The Field Division of the Saranac Laboratory has determined the incidence of tuberculous lesions recognizable in good stereoscopic chest roentgenograms prepared on large groups of workmen engaged in several industries located in various parts of the United States. A preliminary analysis of these groups disclosed that, of 4,012 white male workmen whose roentgenograms exhibited no discernible evidence of occupational dust exposure, 4.76 per cent had tuberculous lesions.

The roentgenological findings for 5,000 steel mill workers were analyzed in detail because their crude incidence rate of 5.24 per cent compared favorably with that for "normals."

The roentgenological findings in 5,000 white male miners were compared with those for the steel mill workers in order to demonstrate the influence which reaction to dust exposure exerts on the incidence of tuberculous lesions.

The incidence of tuberculous lesions has been shown to increase with advancing age, rising among steel mill workers from about 1.0 per cent

at ages less than twenty years to 12.5 per cent for ages from sixty-five to seventy-four.

Evidence has been presented which suggests that the rise in incidence with age is due to the development of new infections at all ages rather than to the survival of groups whose incidence was considerably higher in former years. During the last decade approximately two new cases of pulmonary tuberculosis appear to have developed each year per 1,000 white male steel mill workers. These new cases seem to have developed at any age with about the same facility.

The ratio of incidence of tuberculous lesions to mortality from pulmonary tuberculosis has been found fairly constant at most age groups for white male steel mill workers. This ratio indicates that one death occurs for each eighty cases with recognizable lesions.

Although the ratio of probable incidence to mortality calculated for white male steel mill workers in 1927 remains constant for most age groups, it occurs at a lower level than in 1937. Higher standards of living and improved hygiene appear to offer the worker with a tuberculous lesion a better likelihood of avoiding clinical disease than formerly.

The incidence of tuberculous lesions in Negro and Mexican male steel mill workers has been observed to be about the same as in white males. Apparently lack of inherent immunity accounts for more deaths among Negro and Mexican males with tuberculous lesions than among white males.

Among white miners the incidence of tuberculous lesions has been shown to increase as the degree of reaction to dust progresses. Age has exerted an influence on the incidence of lesions in presilicotic miners but its effect has been overshadowed in the presence of true silicosis where the incidence rates have risen to astonishing levels.

Tuberculosis with silicosis is an occupational disease in seven out of eight miners less than thirty-five years of age, but in only half the miners more than sixty-five years of age.

REFERENCES

(1) WEBB, G. B.: Tuberculosis, Paul B. Hoeber, Inc., New York, 1936.
(2) AGRICOLA, G.: De re metallica, 1556.
(3) HOHENHEIM, THEOPHRAST BOMBAST VON (called PARACELSUS): De restituta viriusque medicinae vera prosi, 1578.
(4) RAMAZZINI, B.: De morbis artificum, Modena, 1700.
(5) DUBLIN, L. I., AND LOTKA, A. J.: Twenty-five years of health progress, Metropolitan Life Insurance Co., New York, 1937.

(6) LANZA, A. J., AND VANE, R. J.: The prevalence of silicosis in the general population and its effect upon the incidence of tuberculosis, Am. Rev. Tuberc., 1934, *29*, 8.
(7) DUBLIN, L. I., AND VANE, R. J.: Causes of death by occupation, Bull. 507, U. S. Bureau of Labor Statistics, 1930.
(8) SAYERS, R. R., *et al.*: Roentgenological appearances in silicosis and the underlying pathological lesions, Pub. Health Rep., 1935, *50*, 989.
(9) KAYSER-PETERSEN, J. E.: Über Reihenuntersuchungen mit Röntgenstrahlen, Ergebn. d. ges. Tuberk.-Forsch., 1937, *8*, 71.
(10) BLOCH, R. G., FRANCIS, B. F., EISELE, C. W., AND MASON, E. W.: Roentgenological group examinations for pulmonary tuberculosis, Am. Rev. Tuberc., 1938, *37*, 174.
(11) FELLOWS, H. H.: A study of incidence of pulmonary tuberculosis, Ibid., 1934, *30*, 109.
(12) FELLOWS, H. H., AND ORDWAY, W. H.: Control of pulmonary tuberculosis in an employee group: possibilities and limitations, Part II, Tr. 33rd Ann. Meeting Nat. Tuberc. A., 1937, 211.
(13) DROLET, G. J.: Present trend of case fatality rates in tuberculosis, Am. Rev. Tuberc., 1938, *37*, 125.
(14) LINDBERG, D. O. N.: A chest roentgen-ray study of the adult Negro population of an entire community, Ann. Int. Med., 1935, *8*, 1421.
(15) Committee on Tuberculosis among Negroes: A five-year study of tuberculosis among Negroes, Nat. Tuberc. A., New York, 1937, 16.

TUBERCULOSIS CONTROL IN INDUSTRY[1]

W. A. SAWYER[2]

Herewith are recorded the results of an effort to control tuberculosis in a group of industrial workers. This dates from 1921 when physical examinations were made on 3,280 apparently well adults, and the detection of tuberculous disease was made an important feature. The chests were examined by means of single films and were diagnosed as either latent, or clinically significant tuberculosis. Those diagnosed as positive (2.4 per cent) or suspicious (1.4 per cent) constituted 3.7 per cent of the whole series and were confirmed by subsequent stereoroentgenograms. This survey revealed cases of previously unsuspected tuberculosis in which there were no clinical symptoms and no diagnostic signs. These cases were all proved by their subsequent clinical course. For the first time the efficiency of the stethoscope, as used in the average physical examination, was seriously questioned. The examination of this group constituted the first phase of our experience.

Prior to this experience, and in common with the majority of clinicians at that time, we had shared the same viewpoint toward the diagnosis of tuberculosis that Ralph C. Matson (1), in a paper on *The Elimination of Tuberculosis From the Army*, described in 1920 as follows:

Mistakes in diagnosis are commonly based on misinterpretation of X-ray findings. The X-ray cannot detect fresh tubercles in the lungs when discrete, and it should be appreciated that careful physical examination generally predicts the roentgenological findings, except in deep peribronchial types of tuberculosis. The roentgenological findings alone are of little value unless interpreted by one having a knowledge not only of roentgenology, but also of tuberculosis from a clinical and pathological standpoint. As compared with the physical examination, the roentgenological examination, even when done by an expert, occupies a place of secondary importance in the diagnosis of tuberculosis of clinical significance.

[1] Read as part of the Symposium on *Tuberculosis in Industry* at the joint session of the Pathological, Clinical, Social Work and Administrative Sections at the 34th annual meeting of the National Tuberculosis Association, Los Angeles, California, June 23, 1938.

[2] Eastman Kodak Company, Rochester, New York.

This was an excellent description of the state of our knowledge a decade ago. But that "doubting Thomases" were even then raising their voices and questioning the relative value of physical examination versus roentgenological examination of the chest for the diagnosis of early tuberculosis, appeared evident in contemporary literature.

Following this survey of 3,280 workers, physical examination of the chests of employees was continued with even greater zeal in a hard-dying effort to match clinical skill in auscultating the human chest, against the efficiency of the roentgenogram, in detecting early tuberculous lesions. This observation is, of course, trite to those of us now engaged in this work, but by too large a part of the profession auscultating is still regarded with traditional veneration as a method of prime importance in ruling out the presence of early tuberculosis.

The second phase of this experience was begun in 1923 when workers and applicants received roentgenological examinations of the chest much more frequently, on the basis of a case-finding program prepared by Dr. Edward Karl Richard. This resulted in a markedly increased efficiency in the discovery of cases of early tuberculosis because clinical history and roentgenograms, through experience, displaced physical examination as the method of greatest effectiveness. However, in spite of our increased alertness, cases of progressive tuberculosis continued to occur in both old and new employees who had been examined repeatedly. These clinically significant experiences brought it forcibly to our attention that even when clinical history and the development of symptoms were relied upon to initiate roentgenological investigation of the chest, all too often a tuberculous lesion would already have progressed to an advanced degree before it was discovered by us. Critical analyses of the clinical records of 69 cases of fatal phthisis, occurring among employees during the years 1920–1930, further emphasized this observation.

Accordingly, late in 1928, which may be regarded as the beginning of the third phase of our experience, we decided to establish the procedure of making routine serial or annual stereoroentgenograms of the chests of all employees and applicants for employment. The anniversary of the date of employment was to be the time for routine repetition of the examination. However, after several years' experience it was found equally satisfactory to follow those over thirty years of age, whose roentgenogram had been negative, at intervals of two or three years. This was, of course, a distinct saving in several ways. At the present

time everyone is roentgenologically checked every three years, and many oftener.

This third and present phase of our program for attempting the early detection and control of tuberculosis among employees in an industrial group has served a two-fold purpose. First, it has demonstrated that it is possible to discover exceedingly early tuberculous lesions of a progressive type and to observe accurately their behavior even in the absence of physical signs and clinical symptoms. This was of such obvious personal benefit to the individuals that its further economic and social advantages need not be here considered. In the second place, this procedure is an excellent means of accumulating invaluable records of scientific merit for the study of the epidemiology and pathogenesis of tuberculosis. It makes available a series of consecutive stereoroentgenograms of the chests of apparently healthy adults, who are somewhat representative of a cross-section of the community in their age groups.

Unfortunately we are unable to indicate the amount of tuberculosis which existed prior to 1921. Physical examinations were not frequent enough and roentgenograms were not made routinely. Many cases of tuberculosis went unrecognized.

VALUE OF ROENTGENOLOGICAL EXAMINATIONS

We were particularly impressed with the value of routine serial or periodic roentgenograms. Before giving the statistical data on the group under supervision since 1928, let us consider briefly some of the practical factors concerning roentgenograms.

Improvements in technical equipment and methods in recent years have materially aided in increasing the effectiveness of the roentgen-ray, making it an excellent medium for our purpose. Twenty years ago Eugene L. Opie and Kennon Dunham expressed the view that it would seem to be not overoptimistic to feel that the diagnosis of pulmonary tuberculosis by roentgenograms, while not infallible, had become a thing of relative accuracy. They also stated that its value does not stop there, for it gives us the means of studying the disease as a scientific problem in its own unfortunate living host.

The stereoroentgenogram was the method chosen in this investigation because of the advantages it offered when compared with results obtainable by use of either the fluoroscopic screen or single films. Subsequently, it was found that single films were adequate in those cases where no pathology had been found.

Single films as a method for selection of individuals for stereoscopic roentgenological investigation are of great usefulness where the question of cost is a deciding factor. They also have the advantage of providing permanent records even when it is not feasible or possible to take stereoscopic films.

Stereoroentgenograms: By means of the stereoroentgenogram it was less difficult for the observers to differentiate between calcified nodules and axially radiated blood vessels, and easier to differentiate between vascular movement and true infiltration. Often one film of a stereoscopic pair will be relatively free from vascular movement as the exposure time changes to coincide to some extent with cardiac diastole. Furthermore, artefacts, in our experience, are easily ruled out, as they seldom occur stereoscopically, but usually occur in a single film of a pair. We have seen this strikingly demonstrated on several occasions. It has been a not uncommon experience to note a definite though very small area of infiltration or a nodule stand out plainly on one film, and be invisible, due to denser overlying substances, on the other film of a stereoscopic pair. This may appear to be of only scientific interest to the investigator, but it may be of excessive and serious importance to the individual under investigation, as we know too well from our clinical experience.

Fluoroscopic examinations: Fluoroscopic examination of the chest in the hands of such capable observers as H. H. Fellows, W. H. Ordway (2, 3), Ada C. Reid, and their coworkers, as a means of selecting employees for stereoroentgenographic investigation in all "positive" and "suspicious" cases, as they do, is of immense practical clinical value. In the hands of inexpert or poorly trained observers, however, the fluoroscope is a potential source of danger to the individual, as clinical experience in private practice has repeatedly demonstrated to us and many other practitioners. Where precise description of latent and extremely delicate early tuberculous lesions is desired for purposes of study and of future accurate comparison of their extent and density, the fluoroscope is obviously inadequate. It is too crude to enable the observer to detect, by means of periodic reëxaminations, those slight though definite progressions and regressions in extent and character of early lesions so graphically depictable on the roentgenogram. The expenditure of time on the part of the physician, and the question of his exposure, confinement and fatigue, under ordinary clinic conditions, are also factors to be considered. Finally, mention might be made of the possible danger of

absentmindedly burning the individual by too prolonged exposure to fluoroscopy.

Another advantage films have in common is that they may be exposed by qualified technicians with a minimum of time loss to the employee at his work, and may be read carefully by the clinician at a time of his choosing. These are entirely practical observations resulting from the type of investigation here described.

TECHNIQUE

Our technique has been changed in keeping with the practical improvements in equipment and technique generally.

We have reviewed our procedures every three or four months with expert technical assistance to insure their maximum effectiveness. It has been our constant endeavor to develop a technique that will take strictly comparable serial roentgenograms over indefinite periods of time. This ideal has not yet been realized, but when proper allowances are made for technical variations we believe the series under consideration represents, in the aggregate, sufficiently comparable films for all the practical clinical and scientific purposes of this investigation. At best the technique and the interpretation of the roentgenogram are but a reflection of the skill and experience of the technician and the physician. No interpretations were based on technically imperfect films. Oblique exposures were made only in special instances where additional information was sought. All the stereoroentgenograms were exposed with the anterior chest against the film. Posterior ribs and interspaces were used for topographical localization of lesions.

TERMINOLOGY AND INTERPRETATIONS

In the early part of our work, that is up until about a year ago, the nomenclatures of Opie and McPhedran were used in our classification. The terms used in the preliminary report of 1931 were: latent tuberculosis, childhood; latent tuberculosis, adult; manifest tuberculosis; and negative. Since that time, for various reasons, the terminology has been changed from latent tuberculosis, childhood to primary complex; from latent tuberculosis, adult to inactive (which includes those arrested for over one year); and from manifest to active or clinically significant.

Any questionable roentgenograms, about which there was disagreement or uncertainty, have been labeled "observation" and serial films made subsequently at frequent intervals to verify the interpretation. No

lesions that could not be demonstrated to an intelligent observer were called positive. By positive we mean those roentgenograms which revealed a primary infection or a parenchymal lesion of the adult type.

The conclusions of McPhedran and of Amberson with respect to "peribronchial tuberculosis" are borne out by our experience. Many of the same healthy adults have had routine roentgenograms made by us during the past seventeen years. The stereoroentgenograms of these individuals were in every instance first interpreted without recourse to previous readings. As a result, we learned that in successive years we would alternately or irregularly describe the roentgenograms of the same individual, who was enjoying continuous good health, as revealing either "peritruncal infiltration or beading of the ascending trunks" or as revealing "no evidence of disease." This forced us to the opinion that "peribronchial infiltrations" and "peritruncal infiltrations" were normal physiological roentgenographic manifestations, rather than evidences of pathological infiltrations of a tuberculous nature.

DIAGNOSES WHICH REQUIRED CHANGE

As the result of the routine serial repetition of stereoroentgenograms of the chests of these apparently well employees, it became necessary in certain cases to change the diagnosis originally made. Films of individuals that had been designated as negative, or as inactive, or as primary complex had on subsequent examinations revealed the development of a very slight though progressive type of tuberculous infiltration, usually in the infraclavicular region, but not uncommonly in the apices or the bases of the lungs. It was these later findings which have necessitated the change in diagnosis in a still increasing number of individuals. Their serial roentgenograms depict the development of the earliest recognizable tuberculous lesions which it is possible to observe and which progress to manifest clinical disease. Our experience with these clinically significant infiltrations, as revealed roentgenologically, has been of two kinds. In the first place, individuals (or the physician) have failed to coöperate to the extent necessary, because of the complete absence of familiar symptoms and signs of ill health. We have been able in these cases, by means of serial stereoroentgenograms, to observe the cold (afebrile) and silent (*sans râles*) advance of such lesions, until, after several or many months, the development of "textbook" signs and symptoms finally established the correctness of the roentgenological diagnosis to the satisfaction of the patient and his physician. This has, unfortunately,

been our not uncommon experience. In the second place, our other experience has been with coöperative employees who immediately followed particular therapeutic instructions, even though they felt perfectly well. In this group it has been possible to demonstrate, in a striking manner in several instances, the rapid retrogression, and sometimes resolution of such infiltrations, and of even small excavations, following absolute rest in bed for a period of from six to twelve weeks.

We are impressed with the enormous economy in time, resources and suffering which a procedure such as this effects. Its benefits not only to the individual and his family, but also to the community, are incalculable.

TUBERCULIN TEST

Up to now we have felt that the intracutaneous tuberculin test was not sufficiently specific in indicating either lesions and their character, or individuals requiring medical care, to aid us in our efforts to discover clinically significant tuberculosis in the age groups under consideration. Inasmuch as the tuberculin test merely indicates infection, and infection is presumably of high incidence in an adult urban industrial group, we have resorted so far only to the roentgen-ray, for we know of no more efficient method for the detection of latent and manifest disease. Such tests might be of value scientifically in determining the incidence of tuberculous infection within the older age groups in the community.

LABORATORY PROCEDURES

Routine laboratory work including sputum, blood and urine examinations was done only on active or clinically significant cases of tuberculosis and on observation cases in which an attempt was made to determine the presence or absence of clinical activity. Serological and cytological studies were not made routinely on this group of individuals.

GENERAL MEDICAL SUPERVISION

All individuals in this group received a comprehensive medical investigation including, of course, a thorough medical history and physical examination. Thus the procedures on which this study is based have formed a small but important part of the general medical supervision accorded to employees.

Coöperation obtained and how: Having the "consent" experience of Hetherington, McPhedran, Landis and Opie (4) and other workers in

mind, we made it a practice in the early years of our experience to hold individual conferences with as many employees and executives as possible prior to making our examination. These personal interviews were for the purpose of getting coöperation and securing statistical data for the study. The opportunity was also afforded for educational talks on the purpose of the examination, the prevalence of infection, the relative infrequency of the disease, and the effective method at our disposal for early recognition of possibly developing disease by means of periodic repetition of the examination. The interested coöperation of the majority was readily secured, although some conscientious objectors had to be won over with an extra effort. Such complete coöperation and good will, so necessary in an adult group of this type, is essential to a continuance of routine investigation. We feel that we could not have secured this had we made intracutaneous tests and blood studies part of the examination at the beginning. This is one important reason why we have postponed these tests, for the psychology of an industrial group at work or seeking employment is decidedly different from that of the clinic, office or hospital patient group.

Information given to employees: Individuals whose chests were negative or whose lesions were of the latent type, clinically insignificant, and only of scientific interest, were informed that their lungs were negative or clear. This practice was followed to avoid the probability of arousing undue concern and to protect employees from possible unjust penalties in their application for life insurance.

Applicants with tuberculous lesions of the primary or inactive types were accepted for employment. We accepted persons with stabilized lesions if clinically negative, whether minimal or moderately advanced in extent. Type of employment, sex and age were influencing factors. We also accepted some cases that harbored small areas of infiltration, soft in appearance and unaccompanied by signs or symptoms. These cases have been examined by roentgenograms at frequent intervals. With the appearance of an increase in the extent of the areas (often occurring more than a year later) the individual was advised to take treatment. This advice was not infrequently disregarded by the patient. When lesions of this kind did not change or decreased in size, the individual was allowed to work under close roentgenological supervision. With the equipment at our disposal, we felt justified in assuming this responsibility. It is questionable whether any other agency can handle this type of case while at work as well as the efficiently organized medical

department of an industrial organization. In the first place, workers in factories seldom can afford the expense of frequent or periodic roentgen-ray studies. In the second place, the workman who feels perfectly well will not voluntarily follow such a program, as it is often distasteful, fear-inspiring and mysterious to him. Third, the inconvenience of distance in repeatedly going to a private office or to clinics with consequent time-loss from work are deterrents for many who require this close supervision but who have not the means, desire or ability to submit to it.

Management of active or clinically significant cases: Where clinically significant or possible active disease was discovered, the employee was referred to his family physician or to a clinic with a complete medical summary of the findings and specific recommendations. When the employee was medically indigent further serial roentgenograms were taken at his physician's request. In every instance the necessity for examining the household contacts of the patient was stressed. In some cases these examinations were made by us. In other instances our visiting nurses made arrangements for such contact examinations to be made at private offices, clinics or dispensaries.

When an arrested patient is able to return to work, it is our practice to have him take up work on a part-time schedule, starting with a few hours a day and increasing gradually until his endurance permits him to work full-time. Whenever possible the employee returns to his former employment.

RECORDS KEPT AND FOLLOW-UP TECHNIQUE

Adequate records were kept and, to insure the return of employees on the dates recommended for follow-up examination and roentgenogram, a tickler file was maintained and was the sole responsibility of one assistant. This has been very effective as a reminder to the clinician to send for individuals on schedule. It was vitally important for the successful conduct of an investigation of this kind.

Any studies concerning clinical tuberculosis, by the very nature of the infection, must of necessity continue over a long period of years and embrace reasonably controllable groups of individuals. Proper and efficient methods to insure continued medical supervision are essential. In the past, our failure to establish early diagnosis and to prevent serious relapses among employees had been due in many instances to clerical error or oversight which resulted in the neglect or breaking of scheduled

appointments by individuals. We had passively allowed them to assume the responsibility for their prompt return for examination. This still is true in private and clinic practice where the control is not as complete as in an industrial group. This control has been strategic for the purposes of this study, to say the least. We believe an accurate and active follow-up technique is a basic requirement for the success of any serious effort to curb tuberculosis. It constitutes vital bookkeeping to guarantee to the individual adequate medical supervision, both for the early detection of such tuberculosis as he may develop and for the control of his arrested disease after he has resumed his work. General appreciation and thoughtful application of this type of supervision for the tuberculous individual commonly encountered in private, clinic and industrial practice will be a great step forward in our preventive efforts. The physician should assume this responsibility in an aggressive and purposeful manner if he is to best serve the needs of the individual. Our colleagues in the dental profession have long given us practical proof of the value of this technique.

A preliminary report of this program was presented in abstract at the annual meeting of the National Tuberculosis Association at Syracuse, New York, May 14, 1931 in collaboration with Dr. Edward Karl Richard. Later work has been done with Dr. John J. Lloyd.

Analyses of several groups will throw some light on the amount of tuberculosis in industry and the liability of workers with minimal tuberculosis.

First, the group which has been under supervision from 1928–1935 and on which the preliminary report was made in 1931, comprising 4,665 employees; second, an applicant group of 4,640 examined from 1935–1938; third, a study of the subsequent course of 75 cases of tuberculosis, known to have cured, after their return to work; fourth, a comparison of mortality in this industrial group with the mortality in the community; and fifth, the morbidity rate since 1923.

EMPLOYEE GROUP

Table 1 gives the incidence of X-ray lesions by type and sex in a group of 4,665 employees.

In chart 1 the distribution of individuals by sex and age is shown. The average age of the women was twenty-eight years, while the average age of the men was thirty-six years. The average age for both was thirty-three years. Of the women, 48.5 per cent were under twenty-five

years of age, while only 20 per cent of the men were under twenty-five years of age.

Chart 2 shows the distribution of tuberculous lesions by age groups.

TABLE 1

Incidence of tuberculosis—revealed by chest stereoroentgenograms—by type and sex, 1928–1935

ROENTGENOLOGICAL FINDINGS	MEN		WOMEN		TOTAL	
	Number	Per cent	Number	Per cent	Number	Per cent
Primary complex	531	17.7	236	14.2	767	16.4
Inactive	457	15.3	156	9.4	613	13.2
Observation	4	.1	6	.3	10	.2
Active	10	.3	14	.8	24	.5
Total positive	1,002	33.4	412	24.7	1,414	30.3
Negative	1,998	66.6	1,253	75.3	3,251	69.7
Total examined	3,000	(64.3)	1,665	(35.7)	4,665	100.0

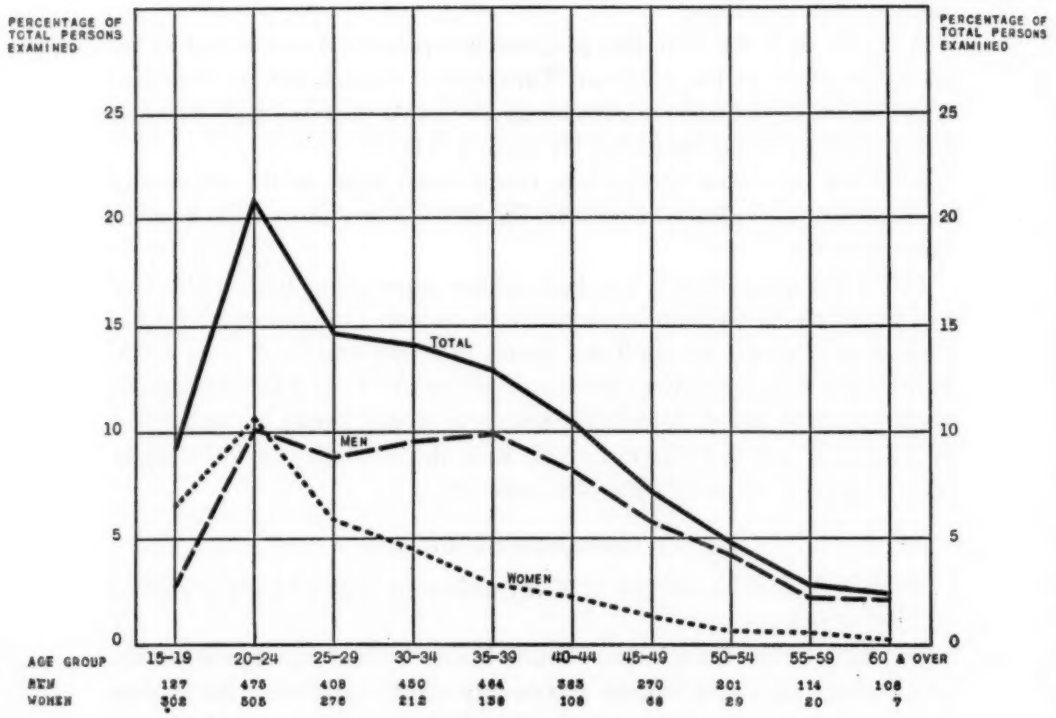


CHART 1. Age distribution of 4,665 persons examined

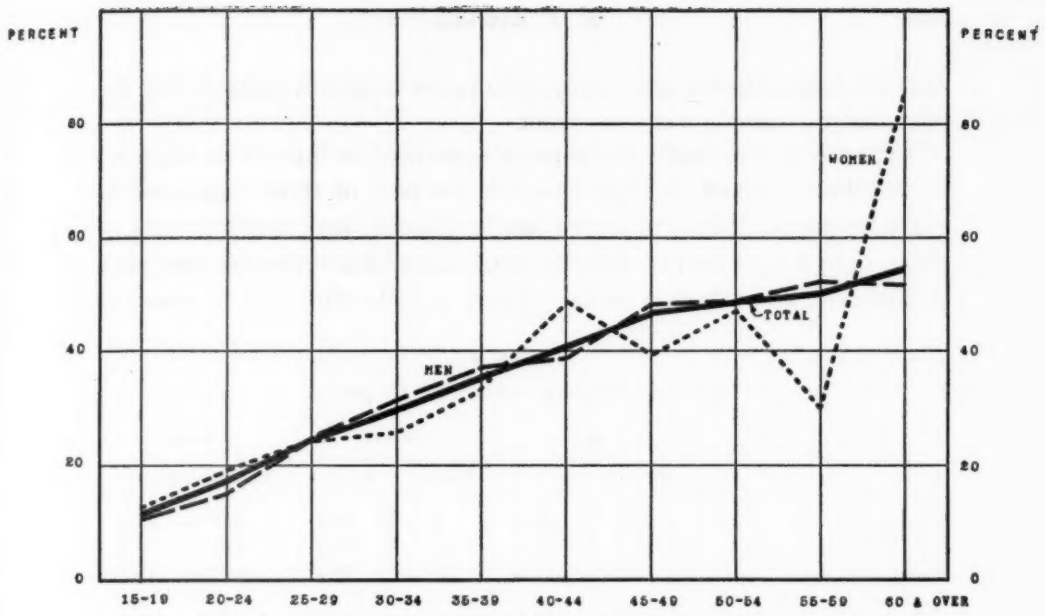


CHART 2. Tuberculous lesions as revealed by chest stereoroentgenograms. Percentage of men and women of various ages showing lesions (based on 4,665 examinations).

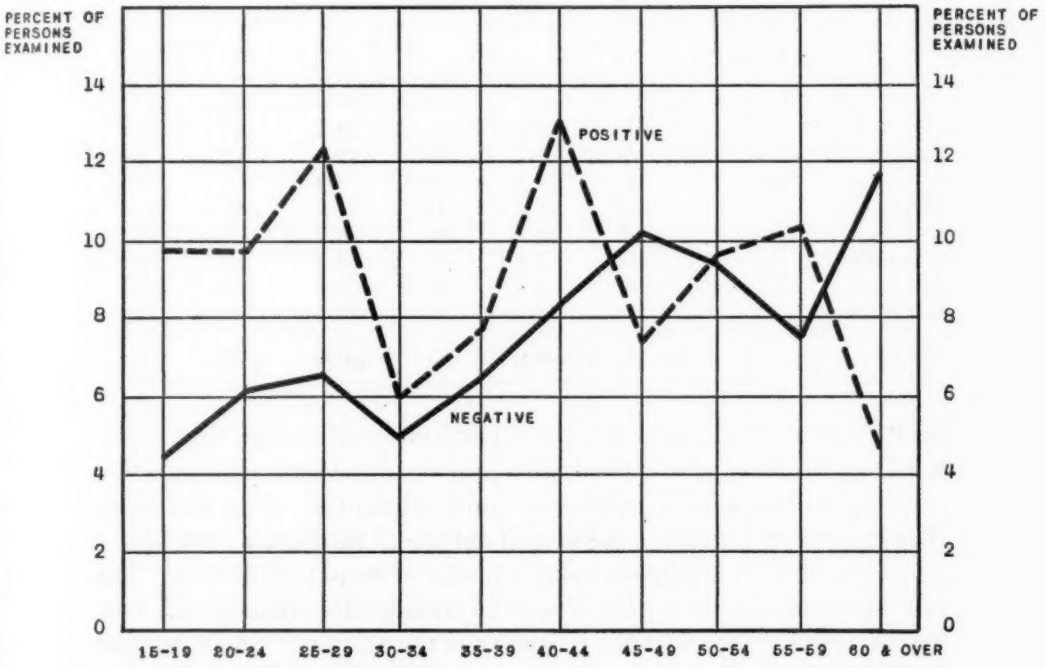


CHART 3. Percentage of 4,665 persons examined exposed to tuberculosis in family, by age and diagnosis.

The fluctuation in the last two age groups for women is explained by the fact that the sample was very small.

Exposure in the family circle has always been of interest in studying tuberculosis. Chart 3 shows that 6.6 per cent of those diagnosed as negative gave a history of known family exposure and, much to our surprise, only 9.3 per cent of those showing tuberculous infection gave such a history. What does it mean? There is little difference in exposure

TABLE 2

Distribution of lesions in lungs of 1,414 persons

LUNG	MEN		WOMEN		TOTAL	
	Number	Per cent	Number	Per cent	Number	Per cent
Bilateral	280	28.0	80	19.4	360	25.5
Left only	295	29.4	123	29.9	418	29.6
Right only	427	42.6	209	50.7	636	44.9
Total persons	1,002	100.0	412	100.0	1,414	100.0

Topographical distribution of 2,271 lesions in 1,414 persons

(4,665 persons examined)

AREA	MEN		WOMEN		TOTAL	
	Number	Per cent	Number	Per cent	Number	Per cent
Right apex	414	25.6	151	23.1	565	24.9
Right middle	51	3.2	72	11.0	123	5.4
Right lower	163	10.1	60	9.2	223	9.8
Right hilum	232	14.3	111	17.0	343	15.1
Left apex	334	20.7	106	16.2	440	19.4
Left middle	121	7.5	35	5.3	156	6.9
Left lower	88	5.4	24	3.7	112	4.9
Left hilum	214	13.2	95	14.5	309	13.6
Total lesions	1,617	100.0	654	100.0	2,271	100.0

between the negatives and positives, particularly at certain ages. One would expect that among those with primary or parenchymal infection there would be a greater number of family exposures. Does this mean that much of our infection is received outside of the home? We hear a great deal about tuberculosis being a family or household disease. The full significance of these data is open to considerable speculation. One has, of course, to consider the reliability of the answers. Small samples in the last three age groups would account for the fluctuation.

Table 2 shows the distribution of lesions. The majority were located in the apex and hilar area.

In the group studied 45.5 per cent of the men and 52.2 per cent of the women were American born or had American born parents. The figures do not seem to show that one nationality is significantly more susceptible to tuberculous infection than another (table 3).

TABLE 3

Nationality of 4,665 persons examined—classified according to roentgenological findings

ROENTGENOLOGICAL FINDINGS	NATIONALITY											
	American		English, Canadian, Irish		German, Scandinavian		Latin, Slavic, Russian		French, Swiss, Belgian		Total	
	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent
Men:												
Primary complex	232	17.0	104	17.0	136	19.2	48	19.5	11	16.9	531	17.7
Inactive	202	14.8	117	19.0	102	14.4	24	9.8	12	18.5	457	15.3
Observation	2	.2	1	.2	1	.1	0	.0	0	.0	4	.1
Active	6	.4	1	.2	1	.1	1	.4	1	1.5	10	.3
Total positive	442	32.4	223	36.4	240	33.8	73	29.7	24	36.9	1,002	33.4
Negative	924	67.6	390	63.6	470	66.2	173	70.3	41	63.1	1,998	66.6
Total men	1,366 (45.5)	100.0	613 (20.4)	100.0	710 (23.7)	100.0	246 (8.2)	100.0	65 (2.2)	100.0	3,000 (100)	100.0
Women:												
Primary complex	108	12.5	70	18.0	43	16.0	6	10.0	9	11.6	236	14.2
Inactive	87	9.9	44	11.3	18	6.7	3	5.0	4	5.1	156	9.4
Observation	5	.6	1	.3	0	.0	0	.0	0	.0	6	.4
Active	8	.9	1	.3	3	1.1	2	3.3	0	.0	14	.8
Total positive	208	23.9	116	29.9	64	23.8	11	18.3	13	16.7	412	24.8
Negative	661	76.1	273	70.1	205	76.2	49	81.7	65	83.3	1,253	75.2
Total women	869 (52.2)	100.0	389 (23.3)	100.0	269 (16.2)	100.0	60 (3.6)	100.0	78 (4.7)	100.0	1,665 (100)	100.0

As might be expected, table 4 shows that there is a higher percentage of positive cases in the underweight groups; the proportion of tuberculous infection increases in both men and women as the percentage of normal weight decreases. There are, however, a significant number of positive cases in the overweight group.

Table 5 indicates that among the men tuberculous infection was quite uniform irrespective of where the individual spent the first ten years of his life.

Among the women there is a considerably higher percentage of positive cases when the first ten years were spent in villages, particularly of those diagnosed as primary complex.

TABLE 4

Weight classification of 4,665 persons examined—classified according to roentgenological findings

ROENTGENOLOGICAL FINDINGS	PERCENTAGE OF NORMAL WEIGHT											
	115% & more		107–114%		94–106%		86–93%		85% & less		Total	
	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent
Men:												
Primary complex..	58	15.5	71	18.3	219	18.5	122	18.8	61	14.9	531	17.7
Inactive.....	33	8.9	32	8.2	180	15.3	114	17.6	98	23.9	457	15.3
Observation.....	1	.3	1	.3	1	.1	1	.1	0	.0	4	.1
Active.....	0	.0	2	.5	1	.1	3	.5	4	1.0	10	.3
Total positive...	92	24.7	106	27.3	401	34.0	240	37.0	163	39.8	1,002	33.4
Negative.....	281	75.3	283	72.7	778	66.0	409	63.0	247	60.2	1,998	66.6
Total men.....	373	100.0	389	100.0	1,179	100.0	649	100.0	410	100.0	3,000	100.0
	(12.4)		(13.0)		(39.3)		(21.6)		(13.7)		(100)	
Women:												
Primary complex..	20	10.9	16	12.2	78	13.5	73	16.8	49	14.6	236	14.2
Inactive.....	6	3.3	4	3.1	52	9.0	42	9.6	52	15.4	156	9.4
Observation.....	0	.0	1	.8	3	.5	0	.0	2	.6	6	.4
Active.....	1	.5	2	1.5	1	.2	7	1.6	3	.9	14	.8
Total positive...	27	14.7	23	17.6	134	23.2	122	28.0	106	31.5	412	24.8
Negative.....	157	85.3	108	82.4	443	76.8	314	72.0	231	68.5	1,253	75.2
Total women....	184	100.0	131	100.0	577	100.0	436	100.0	337	100.0	1,665	100.0
	(11.0)		(7.9)		(34.7)		(26.2)		(20.2)		(100)	

The lower percentage of cases diagnosed as inactive and primary complex with a history of the first ten years' residence in the city is surprising and perhaps significant.

In these 4,665 individuals (table 6) only 15 new cases of clinical significance were uncovered subsequent to the first examination, that is,

from 1928 to 1935. This is 0.3 per cent of the group and seems a rather small amount of new activity in seven years.

Table 6 summarizes the development, method of discovery and present status of these newly developed lesions.

TABLE 5

First ten years' residence of 4,665 persons examined—classified according to roentgenological findings

ROENTGENOLOGICAL FINDINGS	FIRST TEN YEARS' RESIDENCE											
	Country		Village		Town		City		Combination		Total	
	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent
Men:												
Primary complex..	86	20.4	46	18.5	35	15.8	348	17.1	16	21.1	531	17.7
Inactive.....	63	15.0	46	18.5	39	17.6	289	14.2	20	26.3	457	15.3
Observation.....	1	.2	0	.0	1	.4	1	.1	1	1.3	4	.1
Active.....	1	.2	3	1.2	1	.4	5	.2	0	.0	10	.3
Total positive...	151	35.8	95	38.2	76	34.2	643	31.6	37	48.7	1,002	33.4
Negative.....	270	64.2	153	61.8	146	65.8	1,390	68.4	39	51.3	1,998	66.6
Total men.....	421	100.0	248	100.0	222	100.0	2,033	100.0	76	100.0	3,000	100.0
	(14.0)		(8.3)		(7.4)		(69.0)		(25.3)		(100)	
Women:												
Primary complex..	23	16.3	27	28.1	14	13.6	165	13.2	7	20.0	236	14.2
Inactive.....	11	7.8	17	17.7	13	12.6	109	8.8	6	17.2	156	9.4
Observation.....	1	.7	0	.0	0	.0	5	.4	0	.0	6	.4
Active.....	2	1.4	1	1.0	1	1.0	10	.8	0	.0	14	.8
Total positive...	37	26.2	45	46.8	28	27.2	289	23.2	13	37.2	412	24.8
Negative.....	104	73.8	96	53.2	75	72.8	956	76.8	22	62.8	1,253	75.2
Total women....	141	100.0	141	100.0	103	100.0	1,245	100.0	35	100.0	1,665	100.0
	(8.5)		(8.5)		(6.2)		(74.7)		(2.1)		(100)	

APPLICANT GROUP

Here we have an analysis of 4,640 applicants for employment, examined by means of stereoroentgenograms, between September, 1935 and April, 1938. It is interesting to compare this group as shown in table 7 with the group first shown in table 1. The proportion of men to women is about the same, 2 to 1. Only 60.6 per cent of this group were nega-

tive, whereas 68.7 per cent of the first group were negative. In these applicants, 32.1 per cent showed primary infections. This is about twice as many as in the first group. Only 3.4 per cent were diagnosed as inactive, whereas in the first group there were four times as many inactives. One would naturally expect a higher percentage of observation cases in the applicant group. It is here that serial roentgenograms

TABLE 6

Subsequent development of 15 active tuberculosis cases found in a group of 4,665—studied from 1928–1935

DEVELOPMENT		MEN	WOMEN	TOTAL
Negative to	Minimal	1	2	3
	Advanced	0	1	1
Inactive to	Minimal	6	0	6
	Advanced	3	2	5

METHOD OF DISCOVERY	MINIMAL			ADVANCED			GRAND TOTAL
	Men	Women	Total	Men	Women	Total	
By symptoms	2	1	3	1	1	2	5 (33%)
By routine X-ray	5	1	6	2	2	4	10 (67%)

PRESENT STATUS	MINIMAL			ADVANCED			GRAND TOTAL
	Men	Women	Total	Men	Women	Total	
No lost time	1	1	2	0	0	0	
Returned to work	6	0	6	2	1	3	12 (80%)
Working elsewhere	0	1	1	0	0	0	
Not able to work	0	0	0	1	1	2	3 (20%)
Died	0	0	0	0	1	1	

are particularly helpful. One has to get thoroughly acquainted with some cases in this way before a decision can be made. That probably explains 3.4 per cent in the applicants against 0.2 per cent in the older employees. Those diagnosed active were 0.5 per cent in both groups.

The average age of the women in this group was approximately twenty-two years and the average age of the men was thirty years. The average age for both was twenty-seven years. This is a few years

below that of the first group. We did not correlate this group as to age and diagnosis.

Table 8 shows the results of a recent follow-up of 25 active cases in this applicant group. These 25 were rejected for employment.

We have had several outstanding examples which have convinced us that these individuals who have been rejected for employment should follow our advice. One young man ignored the suggestion that he go

TABLE 7

Incidence of tuberculosis—revealed by chest stereoroentgenograms—in 4,640 applicants for employment, September, 1935 to April, 1938

ROENTGENOLOGICAL FINDINGS	MEN		WOMEN		TOTAL	
	Number	Per cent	Number	Per cent	Number	Per cent
Primary complex	970	31.3	517	33.7	1,487	32.1
Inactive	130	4.2	29	1.9	159	3.4
Observation	113	3.6	45	2.9	158	3.4
Active	20	.6	5	.3	25	.5
Total positive	1,233	39.7	596	38.8	1,829	39.4
Negative	1,873	60.3	938	61.2	2,811	60.6
Total applicants	3,106	(66.8)	1,534	(33.2)	4,640	100.0

Age distribution of applicants

AGE	MEN		WOMEN		TOTAL	
	Number	Per cent	Number	Per cent	Number	Per cent
16–25	1,464	31.5	1,321	28.5	2,786	60.0
26–44	1,461	31.5	207	4.5	1,668	36.0
45 and over	181	3.9	6	.1	187	4.0
Total	3,106	66.9	1,534	33.1	4,640	100.0

to the County Sanatorium and secured work elsewhere. Within a year he had a haemorrhage and is now a bed patient in the Sanatorium.

Another applicant was found working in the kitchen of one of the city hospitals after being rejected for employment because of questionable tuberculosis.

Such instances emphasize the need for closer supervision of possible cases of tuberculosis among all workers especially food handlers.

Table 9 shows the course of 75 cases of tuberculosis after curing and

returning to work. This table, of course, verifies the concept that the earlier the diagnosis the better the prognosis. In other words, it is an

TABLE 8

*Present status of twenty-five cases of tuberculosis rejected for employment**

PRESENT STATUS	MINIMAL			ADVANCED			GRAND TOTAL
	Men	Women	Total	Men	Women	Total	
Entered sanatorium	4	0	4	1	0	1	5
Advised to enter sanatorium	1	0	1	1	0	1	2
Examined and being followed by sanatorium	8	1	9	1	0	1	10
No information	3	3	6	1	1	2	8
Total	16	4	20	4	1	5	25

* The average age of this group is twenty-eight years.

TABLE 9

Subsequent course of seventy-five employees who cured for tuberculosis and returned to work

STATUS	MINIMAL			ADVANCED		
	Men	Women	Total	Men	Women	Total
Relapse in 1 year	3	1	4	2	1	3
Relapse in 2–4 years	2	0	2	3	3	6
Relapse in 5 or more years	2	0	2	3	1	4
Total relapsed	7	1	8 (16%)	8	5	13 (52%)
No relapse in 1–5 years	10	5	15	6	1	7
No relapse in 6–10 years	9	6	15	2	0	2
No relapse in 11 or more years	8	4	12	3	0	3
Total not relapsed	27	15	42 (84%)	11	1	12 (48%)

Age distribution at time of original diagnosis

AGE	MINIMAL			ADVANCED			GRAND TOTAL
	Men	Women	Total	Men	Women	Total	
16–25 years	4	5	9 (18%)	2	2	4 (16%)	13 (17%)
26–44 years	21	11	32 (64%)	11	3	14 (56%)	46 (61%)
45 or more years	9	0	9 (18%)	6	1	7 (28%)	16 (22%)
Total	34	16	50	19	6	25	75

argument in favor of early discovery which is the basis of the program we are pursuing.

CHART 4. Tuberculosis, all forms, Rochester, New York. Deaths per 100,000 population, 1900–1937.

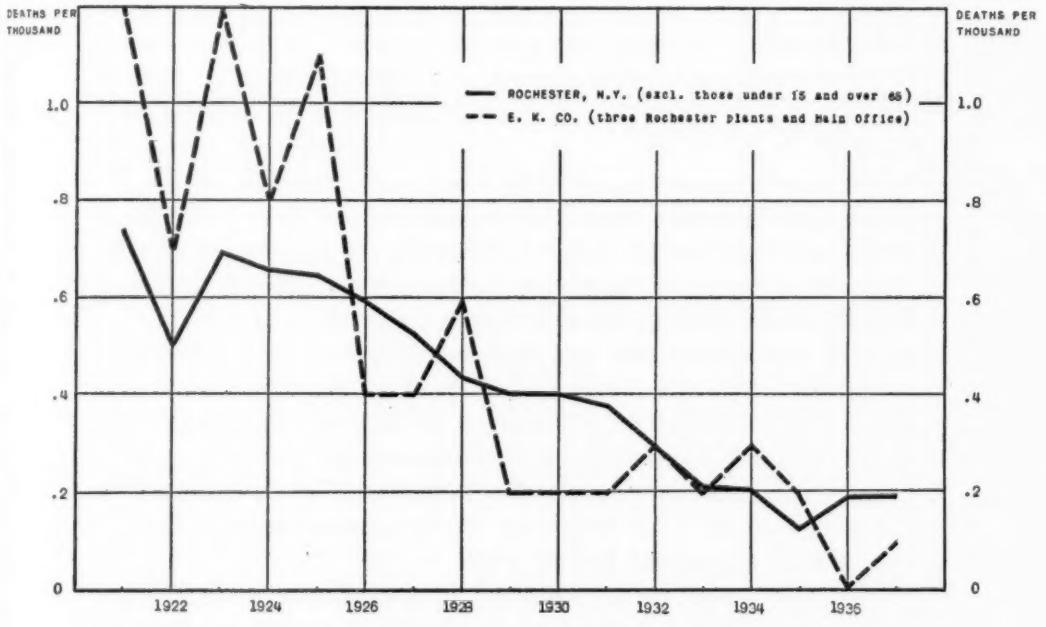


CHART 5. Tuberculosis mortality rate, Rochester, New York and Eastman Kodak Company.

An effort was made to study the absence record on account of sickness of those employees diagnosed as inactive tuberculosis. No definite conclusions could be drawn due to the small number of cases. However, the figures available seemed to indicate that inactive cases as a whole lost more time than the average employee. By separating these inactive cases into three groups, namely, those who never cured to our knowledge (group I), those who cured for minimal tuberculosis (group II) and those who cured for advanced tuberculosis (group III), we find that group I lost approximately the same amount of time as the average employee. Group II lost more time than group I and group III lost more time than group II.

TABLE 10

New cases of tuberculosis causing absence

Three Rochester Plants and Main Office

1923–1937

THREE-YEAR AVERAGE	TOTAL CASES PER 1,000 EMPLOYEES			PULMONARY CASES PER 1,000 EMPLOYEES		
	Men	Women	Total	Men	Women	Total
1923–25	1.95	3.08	2.29	1.89	2.50	2.08
1926–28	1.79	3.61	2.32	1.66	3.00	2.05
1929–31	.80	1.67	1.04	.73	1.67	1.00
1932–34	.58	.43	.54	.49	.43	.47
1935–37	.54	.42	.50	.49	.42	.47

MORTALITY

We have in Rochester, New York a mortality rate from tuberculosis of which we are very proud. Chart 4 shows why, at a glance. Naturally our curiosity was aroused concerning the mortality rate for our employed group which has been under such close scrutiny since 1921.

Chart 5 shows the deaths from tuberculosis per thousand in each of these groups. With proper control the industrial group rate should continue below the city rate. Doubtless the city rate, in part at least, accounts for the favorable rate in this industrial group.

Even more convincing to some of us is the morbidity rate since 1923 as shown in table 10. The three year average shows a decrease in cases per 1,000 employees from 2.08 to 0.47.

At the present time we are following, by periodic check-up, 27 cases of active tuberculosis, 17 of whom are sputum free and working and 10 who are not able to work.

CONCLUSIONS

1. The results of an effort to control and reduce the amount of tuberculosis in a group of industrial workers are here recorded.

2. In the first roentgenological survey made of 3,280 apparently well adult employees in 1921, 2.3 per cent were positive for clinical tuberculosis.

3. Because this survey, roentgenologically, revealed cases of previously unsuspected tuberculosis in which there were no clinical symptoms and no diagnostic signs (râles), the efficiency of the stethoscope in detecting tuberculosis, particularly in its early stages, was seriously questioned by us for the first time.

4. If clinical history and the development of symptoms are depended upon to initiate roentgenological examination of the chest, many cases of early tuberculosis may progress to an advanced stage before discovery.

5. Consequently, in 1928, routine serial or annual stereoroentgenograms of the chests of apparently well adults were made an established procedure for the detection of cases of early tuberculosis, and the detection of early relapse.

6. Tuberculous lesions are found more commonly in males than in females. One-third of the men of these 4,665 individuals showed some signs of infection and only a quarter of the women.

7. In a group of 4,665 employees with an average age of thirty-three years, studied from 1928 to 1935, 0.5 per cent showed active or clinically significant tuberculosis. The occurrence of active tuberculosis is less than was found in the routine flat-film roentgenological examination made in 1921 (2.3 per cent versus 0.5 per cent).

8. In this group, under as near adequate supervision as now seems practical, from 1928 to 1935 only 15 new cases of activity developed. This was 0.3 per cent of the 4,665 employees.

9. In an applicant group of 4,640 presumably healthy adults—average age of twenty-seven years—examined between September, 1935 and April, 1938, there was found 0.5 per cent of active or clinically significant tuberculosis.

10. In a separate study of 75 arrested or inactive cases, 16 per cent or 50 minimal cases relapsed in from one to five or more years. Of the 25 cases of advanced tuberculosis, 52 per cent relapsed over the same period. The earlier the diagnosis, the better the prognosis.

11. An effort was made to study the absence record on account of sickness of those employees diagnosed as inactive tuberculosis. No definite conclusions could be drawn due to the small number of cases. However, those with any signs of tuberculous infection seemed to lose more time than the average employee.

12. The mortality rate of employees, as compared with that of the community in which most of them live, shows a coincident decline in both. The rate per 1,000 individuals of the employed group is below the city rate. Close supervision should produce this result.

13. Morbidity rates since 1923 have been reduced from 2.08 to .47 cases per 1,000 employees as shown by a comparison of three year averages.

14. We believe an accurate and active follow-up technique is a basic requirement for the success of any serious effort to curb tuberculosis. It constitutes vital bookkeeping to guarantee to the individual adequate medical supervision both for the early detection of such tuberculosis as he may develop, and for the control of his arrested disease after he has resumed work.

REFERENCES

(1) MATSON, R. C.: The elimination of tuberculosis from the army, Am. Rev. Tuberc., 1920, *4*, 398.

(2) FELLOWS, H. H., AND ORDWAY, W. H.: Value of routine fluoroscopic examinations of chest among industrial employees, Ibid., 1928, *17*, 201.

(3) FELLOWS, H. H., AND ORDWAY, W. H.: Fluoroscopy versus physical findings in the detection of pulmonary tuberculosis, Part I, and Control of pulmonary tuberculosis in an employee group: possibilities and limitations, Part II, Tr. 33rd Annual Meeting Natl. Tuberc. A., 1937.

(4) HETHERINGTON, H. W., MCPHEDRAN, F. M., LANDIS, H. R. M., AND OPIE, E. L.: Survey to determine prevalence of tuberculous infection in school children, Am. Rev. Tuberc., 1929, *20*, 421.

SURGICAL TREATMENT OF TUMORS OF LUNG AND MEDIASTINUM[1]

FRANK S. DOLLEY[2] AND JOHN C. JONES[2]

It can be truthfully stated that all tumors of the lung and mediastinum are malignant or will become so. Either they are from the beginning carcinomatous or sarcomatous, or they are primarily benign but undergo carcinomatous or sarcomatous change, or, finally, they continue benign to the end but by steady increase in size eventually cause death through circulatory, respiratory or inflammatory complications. Pressure against mediastinal organs or lungs, to any one of which they become so intimately adherent that removal is surgically impossible, renders them therefore actually malignant to the person who supports them.

Six different kinds of thoracic neoplasms from our series are described in this presentation, all successfully removed with apparent complete recovery of the patients.

The symptoms of thoracic neoplasms are almost entirely due to pressure of the tumors upon neighboring organs, resulting in interference with the functions of these organs.

Pain develops if pressure occurs upon a nerve or nerves contiguous to the tumor. If the first thoracic nerve becomes involved, for instance, then pain is present at the base of the neck and, since this nerve aids in the formation of the lower brachial root, there is pain along the ulnar nerve trunk. The intercostals are the nerves most frequently affected so that pressure on one of them, even near the angle of the rib, may refer the pain to the region of the breast, the parasternal region, or even to the abdomen.

Dyspnoea, which is often a prominent symptom, is the result of mediastinal compression by a tumor within it or extensive pulmonary atelectasis, or to a combination of both.

Hoarseness, stridor, brassy cough, irregularity of pulse, etc., all are the result of pressure and their causes are self-evident.

[1] Presented at a joint session of the Pathological and Clinical Sections at the 34th annual meeting of the National Tuberculosis Association, Los Angeles, California, June 21, 1938.

[2] Los Angeles, California.

Diagnosis of a tumor, except a carcinoma deep within a secondary bronchus beyond bronchoscopic visualization, is usually not difficult. The actual type of neoplasm is seldom positively known before its surgical exposure.

The clinical history and physical examination often are suggestive. Fluoroscopic examination and X-ray films are of the greatest value, except in early bronchogenic carcinoma when they are often essentially negative. Negative X-ray films, however, must not halt the physician's consideration of lung cancer, for bronchoscopy is by far the most dependable aid in establishing the absence or presence of bronchogenic carcinoma, and even this is not final since not rarely the carcinoma, early in its symptomatic course, lies deep within the lung and cannot be seen through the bronchoscope. Often lipiodol, delineating the bronchial tree, is of help.

Diagnostic pneumothorax is sometimes of great assistance, for:

1: It enables one under the fluoroscope to ascertain whether the lung is free from the chest wall;
2: Whether the suspected shadow changes in shape and location under air pressure.
3: By means of the thoracoscope one is often able actually to see the growth, particularly if it arises from the chest wall, and to establish tentatively a diagnosis and the most advantageous surgical approach.

Irradiation when sarcoma or Hodgkins' disease exists may rapidly melt away the shadow. It is seldom indeed that such growths would be surgically removable. Such patients would thus be spared operation. It should be emphasized, however, that, if deep X-ray treatment is thought advisable and if the clinical and roentgenological improvement is not convincingly striking, further delay before attempting tumor removal is ill advised. Scar tissue formation following X-ray treatment may soon bind the structures surrounding the neoplasm so intimately to it that complete extirpation may be impossible. The patient should be told that, if following radiation therapy the reduction in the size of the tumor is not considerable, the attempt to remove surgically must not be postponed. Probably all intrathoracic malignant growths found at autopsy to have had a benign origin would have been amenable to successful surgical removal at some time during the course of their development.

The purpose of this presentation is therefore twofold: first, to show that

any intrathoracic growth should be considered benign and therefore surgically removable until it is definitely proved to be malignant; second, to emphasize the fact that an intrathoracic neoplasm, even though proved by biopsy to be malignant, may still be completely extirpated provided there are no evidences of metastases or of direct mediastinal involvement.

Case 1: F. P., female, 36 years old, was referred to us by Dr. Bernard Pearson. There was nonproductive, constant, distressing cough, of eight weeks' duration, high-pitched but not brassy, and occasional pain along the course of the third, fourth and fifth right intercostal spaces. Weight loss was about ten pounds. By X-ray, a clear-cut homogeneous shadow was seen occupying the upper half of the right chest. By means of posterior-anterior and lateral films and corroboration under fluoroscope in various oblique positions the mass was localized as posterolateral. Location and clear-cut isolation from surrounding lung made diagnosis of neurofibroma or a teratoma most likely. It was decided that deep X-ray therapy would needlessly prolong the patient's marked distress with little or no likelihood that radiation therapy would bring even temporary relief.

Operation in July, 1935: Through a posterior curvilinear incision between the scapula and spine the tumor was well exposed. It was found to be a solid mass, firmly adherent to the heads of the ribs and bodies of the vertebrae from the third to the fifth rib inclusive. Its capsule was divided, the line of cleavage found and the tumor was removed without particular difficulty. The patient was discharged on the twelfth day, and, following a short uneventful convalescence, has returned to her former work as housewife.

Microscopical diagnosis: Neurofibroma or ganglioneuroma.

Case 2: I. I., male, 47 years old, referred to us by Dr. R. H. Sundberg of San Diego. In 1919 he was said to have had a lung abscess in the left lower lobe, followed by empyema, later drained by rib resection. He has never felt able to work since. A year later he had a nearly fatal haemoptysis. On three subsequent occasions he bled almost to exsanguination. Some bleeding has occurred every few weeks since that time for sixteen years. Despite persistently negative sputum he was held to be tuberculous and was so treated. Bronchoscopy revealed a slight endobronchial smooth bulging in the left lower lobe bronchus posteriorly. The X-ray film showed a fairly circumscribed shadow in the region of the left lower lobe close to the hilum, made up of faintly concentric layers strongly suggestive of a laminated venous aneurysm.

Operation in September, 1936: Through a posterolateral intercostal in-

FIG. 1

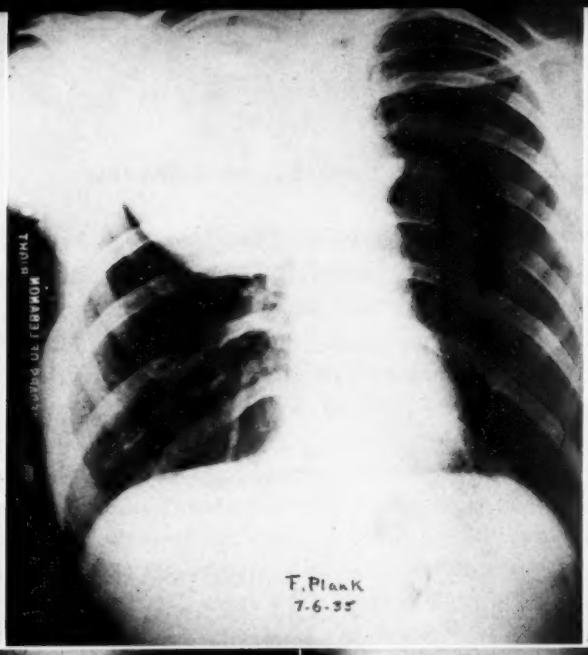


FIG. 2

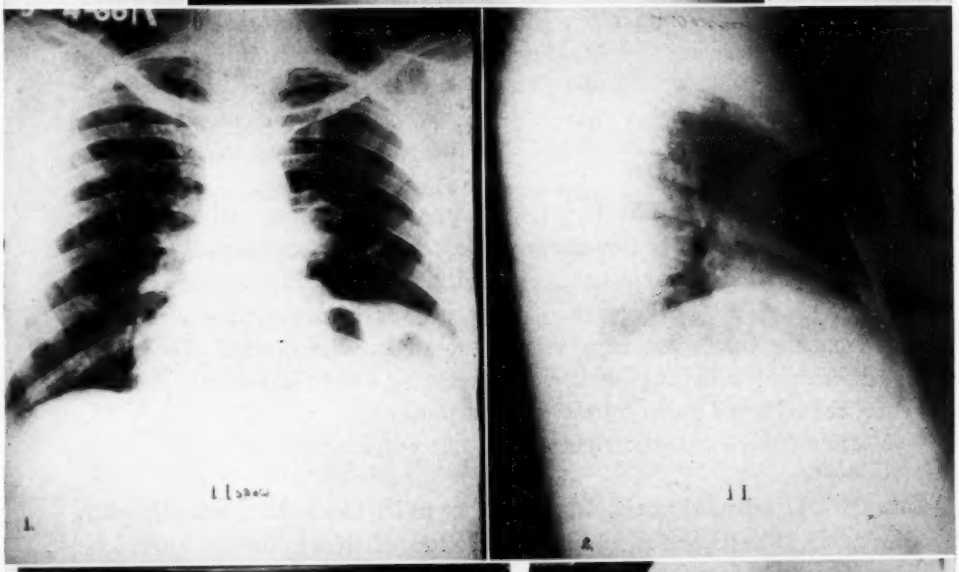
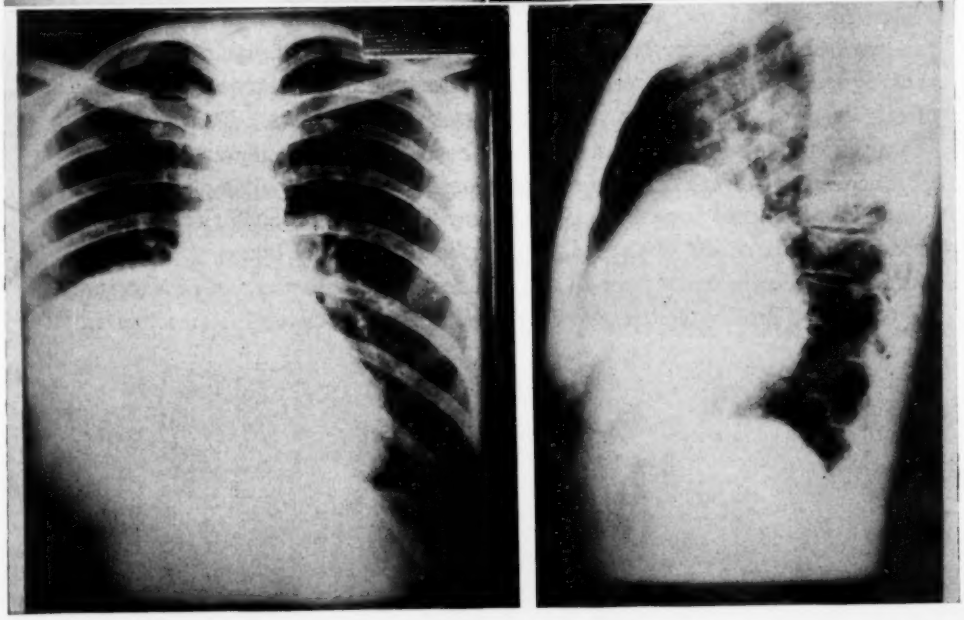


FIG. 3



cision it was found possible to completely extirpate the tumor with the lower lobe without sacrificing the upper lobe.

Microscopical findings: Two sections removed, one largely epithelial composed of solid masses of cells with some gland-like structures, vesicular nuclei with varying amount of cytoplasm. These latter cells show large vacuoles with the intercellular spaces apparently filled with secretion. In some places connective tissue is hyaline with scattered areas of calcification. No mytotic figures are seen. In the other section columnar epithelium is found. Beneath these, an occasional mucous gland is present as if the tumor had originated in the wall of a bronchus and projected into its lumen. The appearance of the cells suggest malignancy as does a great variation in structure of the tumor. While adenomatous charactistics are apparent, yet the general picture very strongly resembles that of a mixed tumor of a salivary gland.

The patient has resumed, after eighteen years of incapacitation, his former work and is apparently entirely well.

Case 3: E. S. B., female, 35 years old. Nine years ago she consulted her family doctor on account of occasional pain in the right lower chest. Diagnosis of heart disease was made and she was told to discontinue all strenuous exercise. There was little change in her condition for eight and one-half years since which time pain became much worse. Dr. Robert Rathbone referred her to us with the diagnosis of intrathoracic tumor.

X-ray films taken in various positions, verified by fluoroscopy, showed a clear-cut homogeneous shadow in the right lower anterior chest immediately above the diaphragm. The clinical history, character of shadow and its location in the lower anterior chest region were strongly suggestive of a dermoid since the majority of these tumors are found in this region.

Operation in January, 1936: Through a curvilinear incision, largely hidden beneath the breast and without rib removal, ample exposure was obtained. A very firm but somewhat fluctuant tumor presented itself. After division of its capsule the line of cleavage was found, and except for considerable adherence to the vena cava no particular difficulty was encountered during the removal of the neoplasm.

Microscopical diagnosis: Dermoid.

FIG. 1. Case 1. Preoperative roentgenogram, July 6, 1935. Dense round homogeneous apical opacity on the right side, filling the upper hemithorax.

FIG. 2. Case 2. Preoperative roentgenograms, September 4, 1936. Rounded opacity the size of a lime in the posterior lobe close to the hilum, extending from the seventh rib to the eighth interspace. High left diaphragm, paralyzed by phrenicectomy done elsewhere for haemorrhage.

FIG. 3. Case 3. Preoperative roentgenograms, January 13, 1936. Dense smooth rounded opacity, filling the anteroinferior aspect of the right hemithorax.

The patient's convalescence was uneventful. In six weeks she drove her car. In three months she was playing tennis. She has remained well since.

Case 4: R. P., male, 13 years old. He was well until six months previous to admission to the hospital. His first symptom was shortness of breath on exertion. Somewhat later nonproductive cough appeared. Gradually dyspnoea became marked. Cough continued nonproductive, brassy in character and almost constant. About three months before admission he developed pain beneath the manubrium which, though never particularly severe, gradually increased. Because of its central location in the mediastinum, malignancy seemed probable. An intensive course of deep X-ray therapy did not appreciably reduce the size of the shadow nor relieve the patient's distress. He was at once referred to us by Dr. Isaac Olch who had supervised his X-ray therapy. Surgical exploration was decided upon.

X-ray films and fluoroscopy in various positions localized the tumor as in the anterior mediastinum, projecting into both lung fields though somewhat more on the left.

In April, 1937, through a left curvilinear incision with division of the costal cartilages, the portion of the tumor projecting into that side of the chest was well exposed. The mass was firm though fluctuant on deep pressure. While it was everywhere adherent to surrounding mediastinal organs and to the lung, there was no sign that it had invaded them. The capsule was divided, a line of cleavage established and gradually, by both blunt and sharp dissection, the tumor was delivered as it lay over the heart and anterior to the aorta. Complete removal was accomplished without great difficulty.

Microscopical diagnosis: Teratoma. There was no evidence that invasion of surrounding structures had occurred.

The postoperative course was uneventful. The patient is now apparently well.

Case 5: W. W., male, 43 years old, referred to us by Dr. David Ghrist. For more than twelve years he had unexplained periods of afternoon temperature, chronic cough and daily production of a little mucopurulent material, always

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FIG. 4. Case 4. Preoperative roentgenograms, February 19, 1937 and April 26, 1937. Barium in the upper oesophagus below which there was a large round dense mass in the anterior mediastinum. The lung fields are clear.

FIG. 5. Case 5. Preoperative roentgenogram, December 16, 1936. Triangular basal shadow suggesting atelectasis of the right lower lobe.

FIG. 6. Case 6. Preoperative roentgenograms, September 19, 1926 and September 13, 1937. Small dense shadow at the fifth rib to left of the spine. Eleven years later large irregular calcification in the same area.

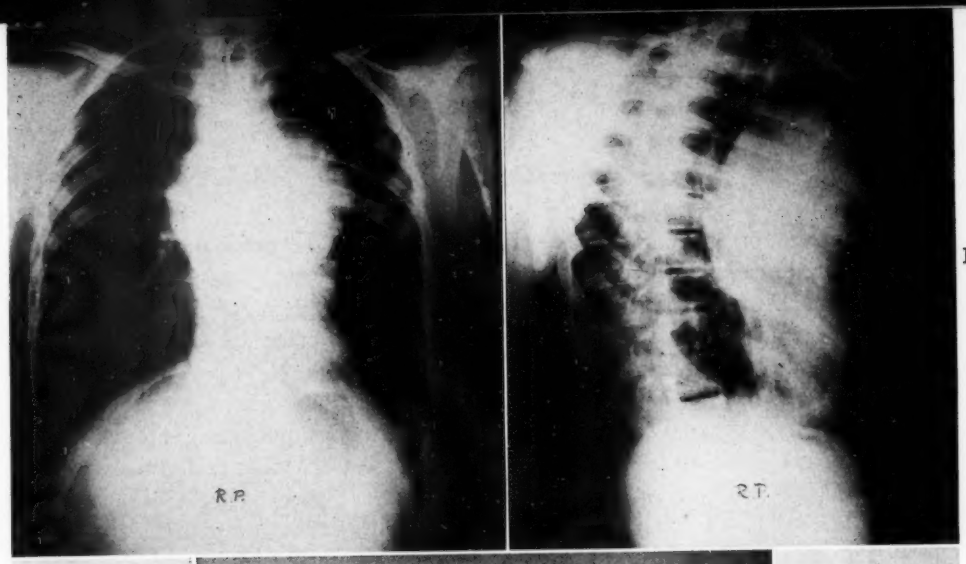

FIG. 4

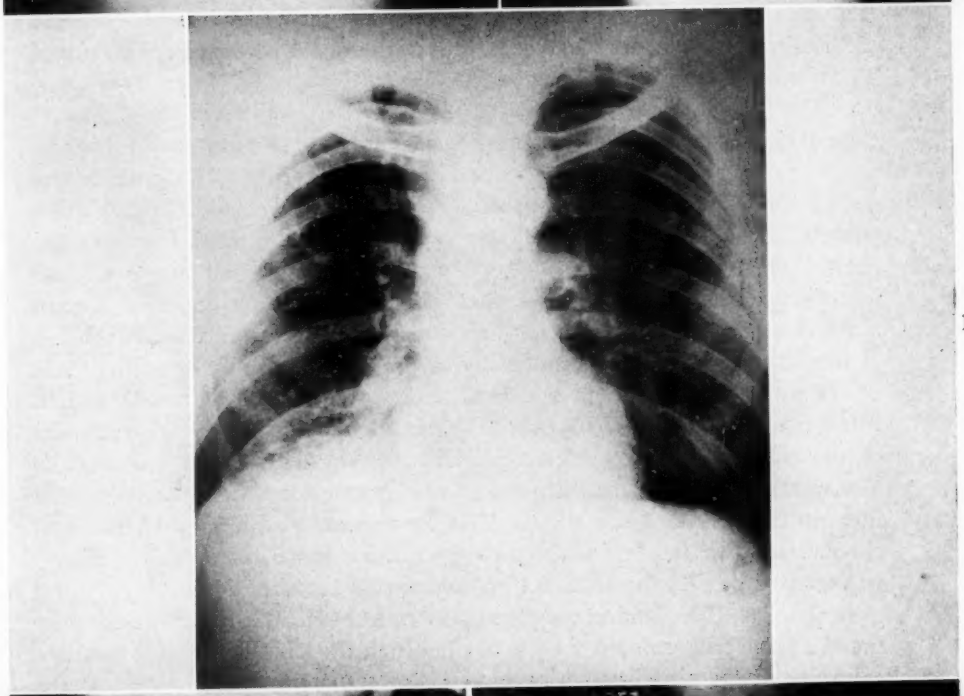

FIG. 5

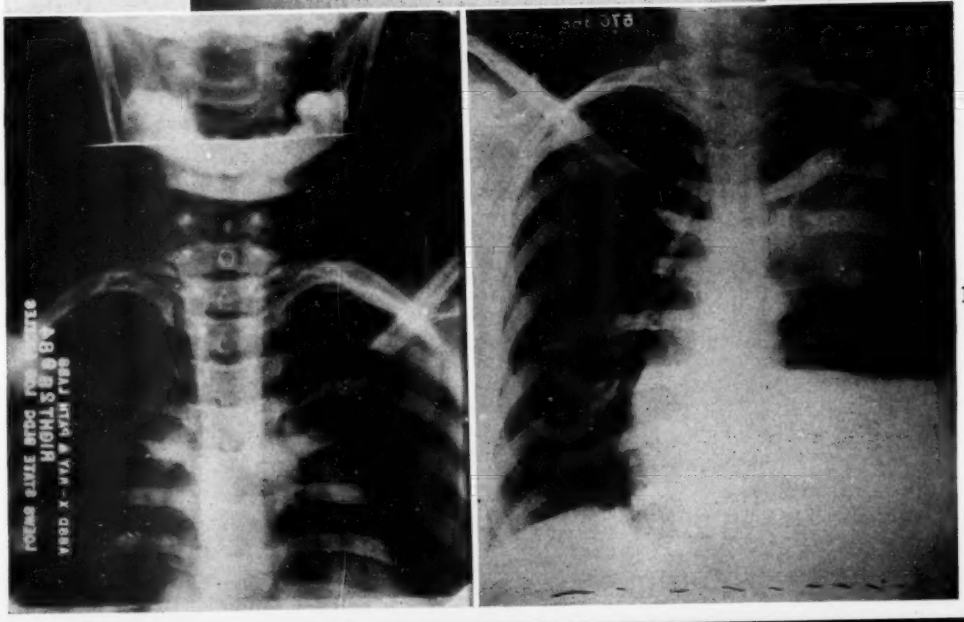

FIG. 6

negative for tubercle bacilli. His sputum was never blood-streaked. A tentative diagnosis of right lower lobe bronchiectasis was made.

Bronchoscopy, following our routine, revealed a red granulating mass in the main stem bronchus at the opening of the lower lobe bronchus. Biopsy showed squamous cell carcinoma.

In January, 1937, complete removal of right lung was performed. The vessels were isolated separately from the main stem bronchus. This was freed in the mediastinum to its bifurcation from the left bronchus and divided 1 cm. distal to it. The stump was completely closed.

The patient's convalescence progressed without untoward event, except empyema which required drainage and subsequent chest wall collapse. Several mediastinal lymph nodes removed at operation did not contain any carcinoma. There is no evidence of recurrence.

Case 6: R. B., female, 21 years old. She complained of numbness in her legs and staggering gait for four weeks and complete inability to walk for several days. Tentative admission diagnosis: Poliomyelitis. Weight loss was fifteen pounds. Two hundred and fifty cc. of blood was aspirated from her left chest. The white count was 40,000 with 92 per cent polymorphonuclear leucocytes. Her temperature was 102.8°F. Her condition appeared serious.

An X-ray film of the thoracic spine shows irregular calcification at the line of the fifth, sixth and seventh dorsal vertebrae and erosion of the left pedicle of the sixth dorsal vertebra and head and neck of the fifth rib on the left. An X-ray film taken eleven years before at the request of her father because of the child's poor posture, which under osteopathic scrutiny revealed no abnormality, shows a small density in exactly the same area, that is, at the fifth rib to the left of the spine. This long established history made osteochondroma with late sarcomatous degeneration more than likely. Biopsy was advised despite the apparent hopelessness of the situation.

In October, 1937, laminectomy was performed by Dr. George Patterson who found a large encapsulated mass extending from the left side, eroding ribs into extrapleural space and compressing the cord. In two stages he cleared the neural canal.

In February, 1938, we resected the thoracic portion of the tumor, involving the spine and left chest wall.

Microscopical diagnosis: Chondrosarcoma.

In March, radiation and physiotherapy were started. In April, the patient began to walk and is now entirely ambulatory. A film taken last month shows no evidence of recurrence. The patient's general condition is steadily improving.

Thus, in these six patients there were as many kinds of tumors. In some there seemed little doubt but that the neoplasms were benign. In others, before operation the diagnosis of malignancy was definitely established or strongly suspected. In all, complete removal was apparently accomplished.

The following statements, therefore, deserve particular emphasis:

1. All intrathoracic neoplasms are or will become either intrinsically or mechanically malignant.

2. Practically all carcinomatous or sarcomatous chest tumors that are found at autopsy to have had a benign origin, were removable at some time during their existence.

3. If radiation is tried and its effect within four to six weeks is not satisfactorily beneficial, surgical exploration must not be delayed, for peripheral scar tissue secondary to X-ray treatment may soon render total extirpation impossible.

4. The operative mortality is very low, the successes are very frequent. If a condition diagnosed as neoplastic exists within the chest, if no metastases are evident, if no involvement of the mediastinum is apparent and no response to X-ray treatment occurs, these patients deserve the benefit of intrathoracic exploration before allowing them to go on to certain inoperability that in the end awaits the possessor of any steadily growing tumor, whether it be malignant or benign. In our series, including those just described, there have been nineteen consecutively successful cases.

BLASTOMYCOSIS[1,2]

(American Blastomycosis, Gilchrist's Disease)

II. A Report of Thirteen New Cases

DONALD S. MARTIN AND DAVID T. SMITH

INTRODUCTION

The case reports of the 347 patients analyzed in part I of this study were scattered among 175 volumes of 92 journals. The largest number of cases reported in one series was 26 and was published by D'Aunoy and Bevan, who described in detail only one patient. The 11 cases reported by different authors in volume 13 of the Archives of Internal Medicine, thoroughly studied by all methods available at that time, did not include data on the serological and allergic status of the patient.

The case histories of our 13 patients have been placed in the following sequence to emphasize certain clinical, immunological, and therapeutic features.

CASE REPORTS

Cases 1, 2 and 3 illustrate the clinical picture of the terminal stages of systemic blastomycosis in which no type of therapy is effective.

Case 1: W. G., no. 4748, colored male of 37, was admitted to Duke Hospital on April 14, 1931, complaining of multiple abscesses for the past seven months. Past history was negative. The present illness began in July, 1930 with periodic attacks of weakness, nausea and vomiting, followed one month later by a "boil" on his forehead. Before rupture and final healing of this lesion, furuncle-like spots appeared on both sides of the nose, the upper lip, both forearms and the right wrist. Over the entire body there appeared in succession new lesions, beginning as round, indurated areas which softened, drained, became crusted and healed with scar formation. He had lost 40

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pounds in weight since the onset of his illness. Urgency and nycturia had developed during the past ten days.

Physical examination: Temperature 39°C. (102.2°F.), pulse 130, respiration 24. He was chronically ill and greatly emaciated. In addition to the skin lesions already described there were large fluctuant subcutaneous abscesses on the right side of the neck, the dorsum of the left hand and left foot, and the outer side of the right foot. Most of the superficial lymph nodes were enlarged. Chest signs and X-ray films suggested thickened pleura over the right base without involvement of the pulmonary parenchyma.

Red cells 1,800,000, haemoglobin 2 g. (13 per cent), white cells 18,450. Differential: polymorphonuclears 95 per cent, large lymphocytes 2 per cent, monocytes 3 per cent. Wassermann negative. Urine: 3+ albumin, many white cells, and some granular casts. Smears of the bloody pus aspirated from the fluctuant abscesses on the left hand and left foot were negative for tubercle bacilli. Blood agar plate cultures, incubated for four days at 37°C., were positive for *Blastomyces dermatitidis*. Sabouraud's cultures streaked from the pus and incubated at 37°C. also were positive, but subcultures on this medium could not be obtained unless it was enriched by the addition of sterile blood. The crinkled, waxy colonies on blood agar were composed of budding yeast-like organisms, and we have maintained the fungus in this yeast-like stage for over seven years by transplanting monthly on blood agar slants. After several subcultures the fungus grew on Sabouraud's medium without the addition of blood. Incubation at room temperature resulted in a white cotton-like growth composed of hyphae bearing lateral conidia. After two years maintenance in the mold-like form, reversion to the yeast-like stage was obtained by transplanting to blood agar and incubating at 37°C. The fungus isolated from this patient fixed complement with sera from cases 3 and 10.

A blood transfusion had to be discontinued because of a severe reaction. The high fever and rapid pulse continued, he weakened rapidly, and died April 21, 1931, seven days after admission. A few hours before death he coughed up a large amount of bloody pus resembling the material previously aspirated from the subcutaneous abscesses, suggesting extension of the infection to the lungs.

Necropsy, performed ten hours after death by Dr. E. B. Craven of the Department of Pathology, showed blastomycosis of skin of face, arms, and legs; large subcutaneous abscesses on dorsum of left foot and right heel; extensive lymphadenitis, especially marked in the inguinal, axillary and neck regions with multiple small abscesses; and bilateral psoas abscesses extending from erosions of the lumbar vertebrae. Abscesses were found in both lungs, the retropleural spaces, the prostate and the spleen. The meninges at the base of the brain were cloudy, and the fungi were seen in the exudate.

Case 2 had a high titre of serum antibodies (indicative of widespread infection), and skin tests showed a state of anergy.

Case 2: V. P., no. 19401, a Negro woman of 28, was admitted to Duke Hospital on May 7, 1936, complaining of sores over the body for three months. Past history was negative. A sister suffered for four years from a chronic ulcerative process on her right arm which had healed with scar formation shortly before the onset of the patient's infection. In February, 1936, the patient had a febrile illness diagnosed "influenza." While she was recuperating there appeared on the popliteal surface of the left knee a small tender "lump" which enlarged rapidly and ruptured spontaneously, liberating a large amount of pinkish gray purulent material. The drainage stopped after a month, but the pain and swelling in the knee confined her to bed. A second abscess, which became fluctuant and drained spontaneously, appeared on the right arm immediately above the elbow. Similar nodules appeared in rapid succession in the subcutaneous tissues of the arms, neck, face and legs. The skin of the face was invaded, resulting in the typical raw fungating appearance of blastomycosis. She developed anorexia, weakness and loss of weight. Two weeks before admission a nonproductive cough appeared.

Physical examination: Temperature 37.8°C. (100°F.), pulse 128, respiration 26, blood-pressure 96/58. The patient was a very emaciated, acutely ill colored woman who held her left knee in semiflexion and complained of excruciating pain. Frequent attacks of spasmodic coughing produced only small amounts of thin mucoid sputum. Over the face and hands were several crater-like ulcers about 3 cm. in diameter with raised irregular borders. The bases consisted of red granulations which exuded sanguinopurulent material. Over the neck, arms and lower legs were many subcutaneous nodules varying from 2 cm. to 6 cm. in diameter which elevated the surface of the skin. Some of the nodules were firm and others were fluctuant and very painful. There was a large subcutaneous abscess on the dorsum of the right hand. The left knee was swollen to twice its normal size, and the tense overlying skin was very tender, causing extreme pain on motion. All of the superficial lymph nodes were enlarged. The mucous membranes of the mouth were ulcerated and covered with necrotic tissue. Chest signs on the right were dulness and diminished breath sounds; moist crackling râles were heard everywhere except at the apex. There were a few moist râles at the left base. The heart was of normal size, the rate rapid with occasional extrasystoles, and the sounds were of good quality. There was a thick purulent vaginal discharge due to an old cervical laceration and chronic cervicitis.

Chest roentgenograms showed an extensive infiltrated area radiating from the hilum toward the medial half of the right lung. The left lung and the diaphragm appeared normal. Roentgenograms of the bones showed destruc-

tive changes in the head of the right fibula and along the joint surface of the left tibia.

Red cells 3,250,000, haemoglobin 5.4 g. (35 per cent), white cells 18,200, polymorphonuclears 95 per cent, large lymphocytes 1 per cent, small lymphocytes 4 per cent. Wassermann and Kahn reactions negative.

Double contoured yeast-like organisms were found in fresh preparations made from sputum, urine, and from pus aspirated from the abscess on the knee. There was none found in the mouth or vaginal secretions. Blood agar cultures of the pus from the knee gave a pure growth of *Blastomyces dermatitidis* after seven days' incubation at 37°C. The patient's serum fixed complement with the strains of *Blastomyces* isolated from cases 6, 10 and 11 as well as with cultures obtained from other laboratories labeled *Endomyces capsulatus*, *Glenospora Gammeli*, *Blastomycoides tulanensis* and *Monosporium tulanense*. Skin tests were negative to the standard heat-killed vaccine and to the fat, protein and carbohydrate fractions of the fungus.

The fever, pulse, and leucocytosis continued, the dyspnoea increased, and she died May 12, 1936, five days after admission.

Necropsy, performed one hour after death by Dr. Roger Baker of the Department of Pathology, showed: caseous blastomycotic pneumonia with small pulmonary abscesses and blastomycotic pleurisy on the right side; blastomycosis of the mediastinal lymph nodes, trachea, and oesophagus; disseminated blastomycotic tubercles and abscesses in the spleen, kidneys, liver, striated muscle, lymph nodes and tonsils; blastomycosis of left knee joint and periosteum and bone of the left tibia; multiple subcutaneous abscesses with sinus formation and cutaneous ulceration; and blastomycotic abscesses of the brain with localized meningitis. Other findings were tuberculous periaortic lymphadenitis, ulcers of the rectum, and terminal dilatation of the heart. Both tubes and the right ovary had been previously removed, leaving old pelvic adhesions and a healed lower abdominal scar.

Case 3 had a weakly positive skin test, a high titre of serum antibodies, and died one month after admission although thoroughly treated with potassium iodide.

Case 3: R. H., no. 53624, a Negro of 24, employee of a North Carolina tobacco factory, was admitted to Duke Hospital on June 14, 1935, complaining of sores on the chest for one year. Past history was negative. In June, 1934, the patient noticed a sore spot on his back between the shoulder blades which increased in size for several weeks, became fluctuant and, after incision by his family physician, was evacuated of about 250 cc. of bloody pus. The lesion continued to discharge purulent material and five and seven months later was followed by similar lesions over the sternum and the right lower chest. The

latter lesions were incised but failed to heal. During the past five months he developed in succession: night sweats, cough productive of yellow purulent sputum, soreness in the chest, dyspnoea and orthopnoea.

Physical examination: Temperature 40.2°C. (104.3°F.), pulse 160, respiration 24, blood-pressure 112/60. The patient was acutely ill and extremely emaciated. Over the upper third of the sternum were two shallow ulcers about 2 cm. in diameter with granulating bases covered with a dirty pinkish exudate. There were draining sinuses in the right midaxillary line and over the third dorsal spine. An area of tenderness was found over the fourth rib beneath the pectoralis major, and there was a moderately tender mass, about 3 cm. in diameter, in the right axilla which seemed to be fixed to the underlying tissues. There was moderate enlargement of all superficial lymph nodes. Chest expansion was limited on both sides but more on the right than the left. There was dulness over the upper lobes of both lungs, and numerous fine and medium moist râles could be heard over the upper two-thirds of the chest. Râles were less numerous over the bases. The heart was normal in size, the rate rapid, and the sounds of good quality.

Chest roentgenograms showed a rather soft uniform mottling throughout the right upper lobe and a similar but less extensive process in the left upper lobe. Roentgenograms of the bones showed localized areas of destruction in the first, second and third ribs anteriorly on the right and in the eighth rib in the midaxillary line. The manubrium and sternum were irregular in outline, and there were large areas of bone destruction along the right margins of the eleventh and twelfth dorsal vertebrae.

Red cells 2,460,000, haemoglobin 8.6 g. (55 per cent), white cells 14,200, polymorphonuclears 69 per cent, eosinophiles 5 per cent, large lymphocytes 4 per cent, small lymphocytes 21 per cent, monocytes 1 per cent. Wassermann and Kahn reactions negative. Urine cloudy, yellow, acid, specific gravity 1.017, albumin 2+, numerous white cells. Double contoured yeast-like bodies present in the urine sediment. Blood sedimentation rate increased.

Double contoured blastomycetes were found by direct examination of the pus from the draining sinuses after clearing with 10 per cent sodium hydroxide, and *Blastomyces dermatitidis* was grown from the pus from the sinuses, the sputum and the urine. The patient's serum diluted 1:32 fixed complement with pure cultures of *Blastomyces dermatitidis* isolated from cases 1, 2, 6, 10 and 11, and the homologous strain. The skin test was 1+ with the standard heat-killed *Blastomyces* vaccine.

Potassium iodide, beginning with 3 drops t.i.d. and increasing by 1 drop t.i.d. until he was receiving 87 drops daily, resulted in no improvement, the temperature and pulse remaining elevated. The leucocyte count remained high with a decrease in the percentage of small lymphocytes and an increase in polymorphonuclear cells and large lymphocytes. He lost weight and

strength and became progressively more dyspnoeic until his death on July 16, 1935, approximately one month after admission.

Necropsy, performed two days after death by Dr. Roger Baker of the Department of Pathology, showed: generalized blastomycosis involving the skin, subcutaneous tissues, lungs, pleura, mediastinal lymph nodes, pericardium, myocardium, endocardium, sternum, ribs, dorsal vertebrae and paravertebral tissues, prostate and left seminal vesicle. Other findings were: right-sided cardiac hypertrophy and dilatation, chronic passive congestion of the liver and spleen, and gelatinous bone marrow. A special report on the pathological changes in the heart and pericardium of this patient has already been published by Baker and Brian.

Cases 4, 5 and 6 illustrate the rapid spread of the disease during treatment with iodides.

The fourth patient in this series had a chronic pulmonary infection, presumably blastomycotic, for five years before admission. He improved slightly during the first three weeks in the hospital, but, after establishing the diagnosis of blastomycosis and inaugurating iodide therapy, the disease spread rapidly and the patient died within four weeks.

Case 4: M. M., no. 2449, a white male of 40, was admitted to Duke Hospital on December 23, 1930, complaining of pain in the chest for the past five years. Past history was negative except for frequent attacks of bronchitis from 1921 to 1925. Pulmonary tuberculosis was diagnosed in 1925 after he developed a severe pain in his chest. After sanatorium treatment for four months, he spent six months as a patient in the Walter Reed General Hospital in Washington, D. C. He improved and returned to work but in January, 1930 was readmitted to the Walter Reed General Hospital for a period of nine months. The sputum was negative for tubercle bacilli, and he was diagnosed "pulmonary tumor of undetermined type," for which he received deep X-ray therapy.

Physical examination: Temperature 39.4°C. (103°F.), pulse 120, respiration 44, blood-pressure 176/70. He had a paroxysmal cough and was emaciated, dyspnoeic and orthopnoeic. The thin chest wall showed little movement with respiration, the accessory muscles of respiration were hypertrophied, and there was retraction of the intercostal spaces on inspiration. Tactile fremitus was increased, and there was dulness and bronchial or tubular breathing over all but the lower half of the left chest posteriorly. Sibilant and sonorous râles were heard throughout the chest, and medium dry râles were heard after expiratory cough over the right lower lobe. Heavy percussion caused severe pain in the chest. The heart was normal in size, the rate rapid and regular, the sounds of good quality, and the second pulmonic and second

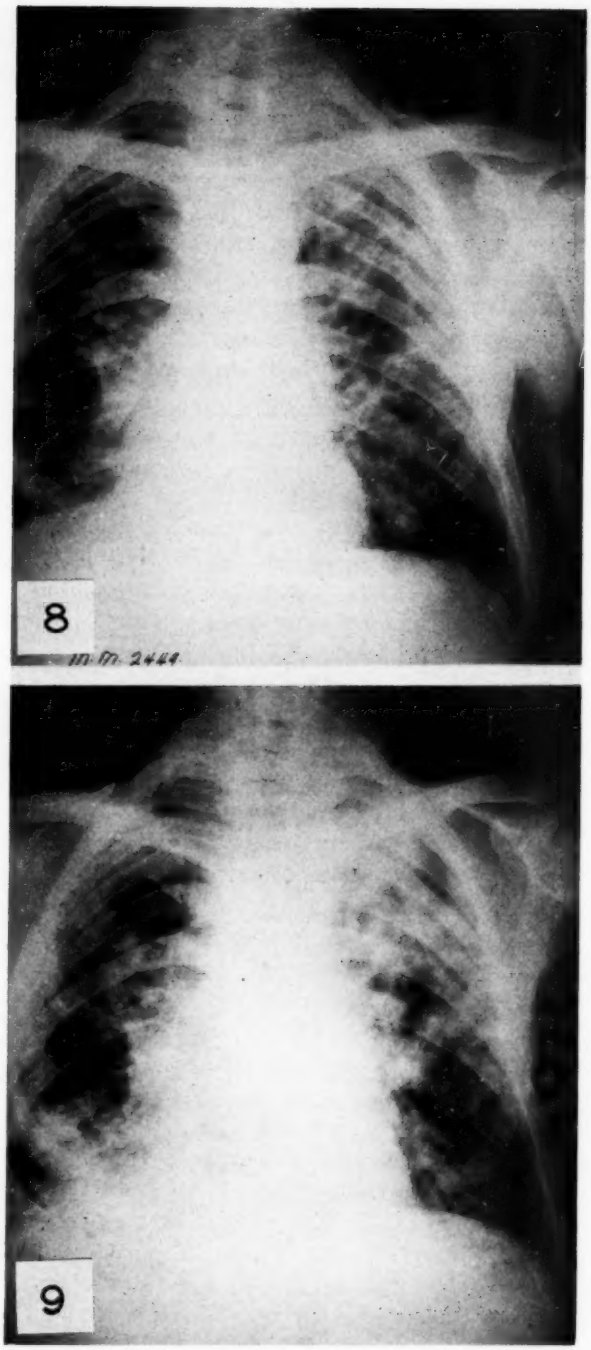


PLATE 2

Rapid spread of pulmonary blastomycosis during iodide therapy (case 4)

FIG. 8. Appearance of lung lesion January 8, 1931, which had shown no change since admission December 23, 1930.

FIG. 9. Appearance of lesion February 11, 1931, after twelve days of oral potassium iodide administration and five days treatment with ethyl iodide inhalations.

aortic sounds were equal. The enlarged and tender liver presented a smooth, sharp edge at the level of the umbilicus. The spleen was palpable 5 cm. below the costal margin, and there was moderate clubbing of the fingers.

Stereoscopic roentgenogram showed extensive dense infiltration throughout the left lung and the lower two-thirds of the right lung (plate 2, figure 8). These films were interpreted by various observers as pulmonary tuberculosis, metastatic neoplasm, fungus infection and Friedländer's bacillus infection.

Red cells 3,430,000, white cells 9,120, haemoglobin 10.2 g. (65 per cent), polymorphonuclears 93 per cent, large lymphocytes 2 per cent, small lymphocytes 2 per cent, monocytes 3 per cent. Wassermann negative. Urine normal.

The patient produced 30 to 50 cc. of mucopurulent sputum daily. Repeated examination failed to reveal tubercle bacilli. *Blastomyces dermatitidis* was cultured after two weeks' incubation on a modified Sabouraud's medium.

The patient improved slightly during the first three weeks in the hospital, and there was a drop in the temperature, pulse and respirations. Potassium iodide therapy was started after isolation of the fungus, beginning with 5 drops of a saturated solution t.i.d. and increasing by 3 drops daily until he was receiving 35 drops t.i.d. Ethyl iodide inhalations, beginning with 0.5 cc. and gradually increasing to 2 cc. daily, were given for ten days but were discontinued because of nausea. The patient became rapidly worse with iodide therapy; the sputum increased, becoming blood-tinged, and the dyspnoea and nausea became more severe. Chest roentgenogram showed extensive and rapid spread of the disease (plate 2, figure 9), and the patient died February 23, 1931, two months after admission.

Necropsy, performed eleven hours after death by Dr. Max Oates of the Department of Pathology, showed blastomycosis of the skin, lungs and liver.

In case 5 the administration of iodides did not prevent the development of subcutaneous abscesses.

Case 5: E. L., no. 32882, a white male farmer of 28, was admitted to Duke Hospital on December 18, 1933, complaining of difficult breathing for six weeks. Past history was negative. In October, 1933, he had a slight pulmonary infection accompanied by lassitude and anorexia, and on November 7, following a chill, he noted a sharp pain in the left chest which was accentuated by deep inspiration. The pain continued and he developed night sweats and a productive cough.

Physical examination: Temperature 38.8°C. (102°F.), pulse 120, respiration 26, blood-pressure 112/60. He was acutely ill, emaciated, dyspnoeic, cyanotic, and the face was flushed. The left side of the chest moved poorly with respiration. The diaphragm was fixed on this side, and the signs over the left lower

lobe were increased tactile fremitus, marked dulness, tubular breathing and numerous fine and medium moist râles. The left upper lobe and the right lung were normal. It was impossible to determine the size of the heart, but the sounds were of good quality and there were no murmurs. The fingers and toe-nails were cyanotic but not clubbed.

Chest roentgenograms showed thickened pleura over the entire left lung, obscuring the diaphragm. A dense uniform shadow at the left base suggested the presence of a small amount of fluid. The pleura over the left side was slightly thickened, and an irregular area of infiltration extended from the right hilum to the region of the right middle lobe.

Red cells 4,260,000, haemoglobin 12 g. (77 per cent), white cells 13,000, polymorphonuclears 87 per cent, eosinophiles 2 per cent, large lymphocytes 2 per cent, small lymphocytes 6 per cent, monocytes 3 per cent. Wassermann negative in December and January; Kahn 1+ and 2+ on both occasions. Urine: trace of albumin, some white cells, a few red cells, and occasional granular and cellular casts.

The sputum which amounted to about 60 cc. daily, was mucopurulent and failed to show tubercle bacilli on repeated examinations. Cultures were positive for *Staphylococcus aureus*, *Neisseria siccus*, and *Streptococcus viridans* and an unidentified species of *Aspergillus*. The tuberculin skin test was negative to 1 mg. of OT. No fluid could be obtained by thoracocentesis.

Iodide therapy was started after finding *Aspergillus* in the sputum. Ten drops t.i.d. of a saturated solution of potassium iodide were increased by 3 drops daily until he was receiving 32 drops t.i.d. at the time of discharge. Ethyl iodide inhalations were given, beginning with 3 cc. and increasing 0.25 cc. daily until he was taking 6 cc. each day. He improved slightly; the fever was less, fluctuating between 37°C. and 38°C. (98.6°F. and 100.2°F.), the sputum decreased, and he gained 5 pounds in weight. Chest roentgenograms on January 9, 1934 showed less infiltration in both right and left lung fields. He was discharged January 21, 1934, thirty-four days after admission, with instructions to continue the potassium iodide by mouth and to return in one month.

He was readmitted to the hospital on February 8, 1934, complaining of swellings over the right jaw and right hip. He had taken the iodide since discharge, and although his dyspnoea and sputum had practically disappeared, other symptoms developed. He had a severe watery diarrhoea, lasting for a week, followed by the development of a red painful swelling over the right ilium. A nontender fluctuant swelling also developed below the right mandible. One week before readmission his cough returned, and he raised 30 to 60 cc. of purulent sputum which occasionally contained blood.

There was dulness over the left lower lobe, and moist crackling râles were heard over this area. Chest roentgenograms showed the lesion in the right

hilum to be stationary, but the process in the left lung had cleared considerably with some thinning of the previously thickened pleura. Roentgenograms of the bones showed a large area of destruction in the right ilium extending from the anterior spine downward and backward for a distance of about 5 cm. Similar but smaller areas of rarefaction were present in the head and neck of the right femur and beneath the right jaw. Bloody pus was obtained from the abscesses when they were incised and drained on February 10, 1934. *Blastomyces dermatitidis* was seen and cultured from the sputum and from the contents of the abscesses. The sputum was negative for aspergilli. His blood serum fixed complement with his own organisms and with cultures isolated from case 6. His strain of fungus was used as antigen in complement fixation tests with sera from cases 3, 6 and 10. Endermal injection of an autogenous *Blastomyces* vaccine produced an immediate urticarial response but no delayed tuberculin-like reaction.

Vaccine treatment was started with 0.1 cc. of a 1:1000 dilution of the autogenous blastomyces vaccine, increasing the dose by 0.1 cc. every second day. He also received large amounts of iodides. The sinus in the hip remained open; the cough, sputum, dyspnoea and fever continued, and he was discharged March 28, 1934 with instructions to continue taking 40 drops of potassium iodide t.i.d. and 6 cc. of ethyl iodide by inhalation.

When next seen, April 11, 1934, the abscess in the neck was still present. The sinus in the hip was closing by granulation, but roentgenograms showed increasing bone destruction. He was much weaker and the prognosis was considered hopeless. We later learned that he lived until May, 1935, approximately two and one-half years after the onset of his disease. No details could be obtained of the last year of his illness, and necropsy was not performed.

In case 6 the patient developed new foci in the lungs and developed additional lesions in the bones while taking iodides.

Case 6: S. D., no. 29178, a colored farm boy of 16, was admitted to Duke Hospital on September 5, 1933, complaining of ulcer on side for one year. In June, 1932, a small, slow-growing, painless swelling appeared near the left nipple. It attained the size of a "hen's egg" by October, 1932 and, after becoming fluctuant, was incised by his family physician. The wound continued to discharge, excessive granulation tissue appeared, and in February, 1933 curettings of the sinus were sent to the Department of Pathology of Duke Hospital, where a diagnosis of blastomycosis was made. The lesion decreased rapidly in size after curettement, but within a few months another sinus appeared lateral to the original lesion. After the development of the second sinus he began to cough, raising purulent sputum which gradually increased to about 60 cc. daily. The sputum frequently was streaked with blood during

the four weeks preceding admission. He lost 20 pounds in weight and was moderately dyspnoeic.

Physical examination: Temperature 39°C. (102.2°F.), pulse 110, respiration 34, blood-pressure 124/82. He was poorly nourished and moderately dyspnoeic but in no pain. On the left anterior chest wall, about 5 cm. below and to the left of the nipple, was a shallow, irregularly shaped ulcer with undermined edges and a dirty granulating base which exuded a purulent discharge. There were several draining sinuses in this region. The respirations were rapid but regular, and expansion was good. Over the lower left lobe were heard many fine moist râles with diminished tactile and vocal fremitus and decreased breath sounds. The right lung and the left upper lobe appeared to be normal. The only cardiac abnormality was an increased second pulmonic sound.

Chest roentgenograms showed an extensive soft infiltration throughout both lungs, more extensive on the left. There was a small amount of fluid at the left base and enlargement of the nodes in the upper mediastinum.

Red cells 5,300,000, haemoglobin 10.2 g. (65 per cent), white cells 8,300, polymorphonuclears 71 per cent, eosinophiles 4 per cent, large lymphocytes 2 per cent, small lymphocytes 22 per cent, monocytes 1 per cent. Wassermann negative. Urine normal.

The sputum was thick, purulent and blood-tinged. *Blastomyces dermatitidis* was found in fresh preparations and cultured from the sputum and the chest wall lesions. Repeated examinations failed to show tubercle bacilli. The patient's serum fixed complement with the homologous strain and cultures from cases 3, 5 and 10.

Potassium iodide was started September 6, the day after admission. He received 20 drops of a saturated solution t.i.d., increasing 3 drops daily until he was receiving 45 drops t.i.d. Ethyl iodide inhalations were started on the second day after admission, receiving 3 cc. b.d. He improved slightly during the first two weeks of treatment. The sputum decreased in amount and his dyspnoea diminished, but the roentgenogram showed an extension of the process in the left lung. His temperature remained between 38°C. and 39°C. (100.3°F. to 102.3°F.), and he failed to gain weight. Medication was discontinued for a week because of an iodide rash which developed after three weeks of treatment. Lipiodol, injected into the sinuses on the chest, did not penetrate into the lung. The infection in the lungs extended, and erosion of the third and fourth ribs on the left side was found by roentgenogram December 27, 1933.

Beginning January 22, 1934, a series of intravenous injections of Fuadin was given without benefit and was soon followed by a series of subcutaneous abscesses over the back. *Blastomyces dermatitidis* was isolated from these lesions. Chest roentgenograms April 27, 1934 showed involvement of most

of the ribs on the left side and extension of the infection to almost all of the lung tissue. The liver became tender, the temperature increased, the white cell count varied from 19,000 to 30,000, and casts and albumin appeared in the urine. The fever disappeared during the last two weeks of life, but morphine was necessary to control the dyspnoea and increased pain. Massive oedema of the legs appeared, and he died May 23, 1934, eight months after admission, and two years after the onset of the infection.

Necropsy, performed three days after death by Dr. A. Smith of the Department of Pathology, showed: blastomycosis of both lungs and of the tracheobroncheal lymph nodes, and blastomycotic osteomyelitis of the left ribs posteriorly; pleural adhesions on the right side and a bronchial fistula on the left; blastomycotic obliterative pericarditis extending through the wall of the right auricle, forming an ulcerative tubercle in the endocardium. There were several subdiaphragmatic abscesses, and blastomycetes were found disseminated throughout the liver. Other findings were hypertrophy and dilatation of the right ventricle with hydrothorax on the right, ascites and hyperplastic bone marrow. The pathological changes in the heart have been described and discussed by Baker and Brian.

Cases 7, 8 and 9 illustrate the findings in patients who, when first seen, were in good physical condition and theoretically should have responded well to therapy.

Case 7, although infected for six years, had not become hypersensitive to the fungus and developed no antibodies.

Case 7: P. S., no. 80437, a Negro laborer of 34, was admitted to Duke Hospital on February 16, 1937, complaining of sores on right foot, left ear and left side of the face for six years.

In 1929, seven years before admission, the patient noted increasing deafness in the left ear. He had some night sweats about this time but no cough or loss of weight. In 1931, a small pimple appeared on the inner side of his right heel which increased slowly for three weeks and spontaneously discharged slightly yellowish pus. In a year and a half this lesion had grown to a diameter of about 3 cm., and two smaller ones appeared near the original lesion. In 1934 the three lesions were excised and healed promptly. By this time he was totally deaf in the left ear, and a furuncle in the canal was found by his local physician. Six months later there appeared on the dorsum of the right foot and on the auricle of the left ear two small pimples, similar to the original lesion, each of which progressed in the same manner, developing fungating granulations which exuded a yellow purulent material. In 1935, after a blow on the left side of his head in the region of the skin lesion, there developed a tender swelling behind the left ear which soon opened and discharged con-

siderable pus. All of the lesions were progressing slowly at the time of admission.

Physical examination: Temperature 37°C. (98.6°F.), pulse 80, respiration 18, blood-pressure 134/70. The patient was well developed, well nourished, and did not appear ill. A crusted fungating lesion, 1 x 4 cm., extended from the left ear to the face, destroying the lobe of the ear. Posterior to this organ was a depressed lesion with a sinus partly covered by crusts. A similar lesion, 4 cm. in diameter, was present on the dorsolateral side of the right foot. There were three scars over the right heel and along the inner side of the right foot. The left ear was deaf to air and bone conduction, there was a serous discharge, the canal was almost closed, and the ear drum could not be seen. The superficial lymph nodes were moderately enlarged. The chest was well formed but expanded poorly. There were no physical signs of pulmonary disease. The heart was normal in size, and the sounds were of good quality. The spleen was palpable, but the liver and kidneys could not be felt. There was a right inguinal hernia and some relaxation of the left inguinal ring.

Chest roentgenograms showed the lungs to be clear, but there were masses of mediastinal lymph nodes extending downward over the ascending aorta, completely filling the superior mediastinum. There was complete destruction of the mastoid cells on the left. Stereoscopic films of the skull showed a generalized loss of calcium and an area of bone destruction, 8 cm. in diameter, in the left parieto-occipital region.

Red cells 3,630,000, haemoglobin 12.4 g. (80 per cent), white cells 5,600, polymorphonuclears 54 per cent, basophiles 4 per cent, large lymphocytes 29 per cent, small lymphocytes 11 per cent, monocytes 2 per cent. Urine normal. Wassermann negative. Intracutaneous tuberculin test negative to 0.1 mg. of OT.

Double contoured, yeast-like bodies resembling blastomycetes were found in fresh preparations from the lesions on the face and foot. *Blastomyces dermatitidis* was isolated from the lesion on the face. Skin test with heat-killed *Blastomyces* vaccine was negative, and there was no fixation of complement with a mixed *Blastomyces* antigen.

Treatment was started with local applications of copper sulphate and potassium iodide by mouth, but the patient became discontented with the hospital routine and was discharged against advice March 1, 1937, two weeks after admission.

Case 8 improved rapidly with iodide therapy in the hospital and continued to improve for six months after discharge, at which time he was apparently well and iodide therapy was discontinued. After remaining in good health for a year, he relapsed and died.

Case 8: L. W., no. 1038, a Negro boy of 12, was admitted to Duke Hospital on September 29, 1930, complaining of sores on the back of neck and right leg for three years. Three years before admission there appeared, on the back of the neck and on the right leg below the knee, small red papular lesions which gradually progressed until they became large open granulating sores.

Physical examination: Temperature 38.2°C. (101°F.), pulse 116, respiration 24, blood-pressure 98/60. The patient was well nourished and did not appear ill. On the back of the neck was a lesion 5 x 10 cm., characterized by red granulations, elevated 0.5 cm. above the surface of the surrounding skin, and a smooth, hard, definitely elevated border. There was some superficial ulceration of the granulation tissue. A similar lesion was found immediately below the right knee. The regional lymph nodes of the neck and leg were enlarged, and there was enlargement of the nodes in both groins and the right axilla. The rest of the examination, including the thorax, was negative, but stereoscopic roentgenograms of the chest showed a soft, diffuse infiltration extending throughout both lungs from the level of the first interspace to the diaphragm. The pictures were similar to those seen in some types of miliary tuberculosis.

Red cells 3,810,000, haemoglobin 10.5 g. (76 per cent), white cells 7,400, polymorphonuclear 76 per cent, eosinophiles 4 per cent, small lymphocytes 14 per cent, large lymphocytes 4 per cent, monocytes 2 per cent. Wassermann negative. Urine normal.

A biopsy, taken from the edge of the lesion on the leg, showed the typical picture of blastomycosis. *Blastomyces dermatitidis* was cultivated from the ulcer on the leg.

The superficial secondary infection was treated by local applications of hydrogen peroxide and gentian violet. The lesion on the neck received two small doses of X-ray. Potassium iodide, administered by mouth, beginning with 4 cc. of a 10 per cent solution t.i.d. and gradually increasing to 10 cc. t.i.d., was taken without difficulty. He continued to have slight elevations of temperature varying from 37°C. to 38°C. (98.6°F. to 100.2°F.), the pulse remaining between 100 and 112. He was discharged October 15, 1930, sixteen days after admission, with instructions to continue treatment with 3 g. of potassium iodide daily. Although the iodide was not taken regularly at home, the lesions were somewhat smaller on his readmission January 19, 1931. The roentgenographic shadows in the chest had not changed during this three month interval. The patient was placed on the same regimen as on the first admission except that the oral administration of potassium iodide was supplemented by ethyl iodide inhalations, beginning with 2.5 cc. and gradually increasing by 0.5 cc. increments until he was receiving 5 cc. daily. After two weeks of treatment there was marked improvement in the lesions, and at the

time of discharge, March 14, 1931, the lesion on the leg was practically well and the one on the neck had decreased to less than half the original size. Chest roentgenogram on discharge showed a remarkable clearing of the pulmonary lesions.

A letter from his family physician, six months later, stated that the leg lesion was entirely well and the one on the neck had reduced to an area of 3 x 3 cm. He received no more treatment, and, after remaining in good health for about a year, his physician reported that he developed extensive involvement of the lungs and died, presumably of blastomycosis.

Case 9 was inadequately treated with iodides, and, although he had a slowly progressive disease for four years, he did not become hypersensitive and developed no antibodies.

Case 9: G. J., no. 22791, a white male farmer of 53, was admitted to Duke Hospital on February 27, 1933, complaining of sores on face, right shoulder, arm and leg for two years. He was apparently well until February, 1931, when a few papules appeared on the right wrist, right ankle, right shoulder and over the face. The papules became pustular, slowly spread, and became surrounded by dull red areas. As the process extended into the advancing red margin the skin became dry, then scaly, and finally piled up in hard, crusted, elevated masses. About six months after the onset he was treated for two months by oral administration of a colorless liquid medicine which had a salty taste. The lesions retrogressed rapidly, but he discontinued medication before they had entirely healed. For the past eighteen months the disease had progressed slowly but steadily.

Physical examination: Temperature 37.4°C. (99°F.), pulse 78, respiration 24, blood-pressure 160/65. The patient was well nourished, well developed, and not acutely ill. The lesions over the right arm, face and ankle were annular, elongated, and fungated with piled-up brownish edges. The process was apparently healing in the centre and spreading at the edges (plate 3, figures 10, 11 and 13), leaving a flat white scar surrounded by a secondarily infected active elevated crusted area. The skin immediately surrounding the lesion was dull red in color. Some of the early lesions on the face had healed with scars which retracted the lips to the right and pulled the left eyelid to the left. The lesions on the shoulder had healed, leaving two large white scars. There were many dilated capillaries over the face. The retinal vessels were tortuous, the teeth in poor condition, and the tonsils enlarged and hyperaemic. There was marked carotid pulsation. The heart was slightly enlarged, and a low pitched systolic murmur at the apex was transmitted to the anterior axillary line. The radial and tracheal arteries were thickened and the liver was slightly enlarged. The lungs were normal except for a few moist râles at the bases posteriorly. The prostate was slightly enlarged and indurated.

PLATE 3

Skin lesions of blastomycosis (case 9)

FIGS. 10, 11 & 13. Appearance of skin lesions February 28, 1933.

FIG. 12. Appearance of face February 21, 1935.

Chest roentgenograms showed only generalized fibrosis and pleural thickening over the apices.

Red cells 3,350,000, haemoglobin 10.3 g. (66 per cent), white cells 8,300, polymorphonuclears 81 per cent, eosinophiles 1 per cent, basophiles 1 per cent, large lymphocytes 7 per cent, small lymphocytes 8 per cent, monocytes 2 per cent. Wassermann negative. Urine showed 2+ albumin and a few white cells.

Large numbers of double contoured bodies resembling *Blastomyces dermatitidis* were seen in smears of the skin lesions, but cultures for blastomyces were unsuccessful, probably because media containing blood were not used. Histological section of tissue removed at biopsy was characteristic of blastomycosis of the skin.

The secondary infection of the skin lesions was treated by thorough mechanical cleansing and applications of chlorozene ointment. Potassium iodide by mouth, beginning with 3 drops of a saturated solution t.i.d., was increased 3 drops daily until he was receiving 30 cc. t.i.d. At the same time he was given ethyl iodide inhalations, beginning with 1 cc. daily and gradually increasing by 0.5 cc. increments until he was receiving 6 cc. daily. The lesions on the face and arm showed definite improvement, but the one on the ankle showed no change. He was given three erythema doses of X-ray just before discharge. He was discharged March 23, 1933, four weeks after admission, with instructions to continue the potassium iodide treatment and to return in one month.

The patient returned June 12, 1933 for additional X-ray therapy. There was no appreciable change in the lesions at this time. On his third admission, February 21, 1935, twenty months later, he stated that his disease, after remaining stationary for about eight months, had spread rapidly during the past year. Contractures resulting from scar formation had kept him in bed. Physical examination showed hideous deformities (plate 3, figure 12). The eyelids were scarred and contracted, the mouth could be opened only partially with great difficulty, and most of the nose had been eroded. The extensive lesions scattered over the body were not dissimilar to an advanced case of leprosy. Chest roentgenogram showed no extension of the disease to the lungs.

Scrapings from the skin, inoculated on blood agar plates and incubated for ten days at room temperature, resulted in a white cotton-like growth which was contaminated with cocci. A pure culture of the yeast-like stage of *Blastomyces dermatitidis* was obtained by clipping the tops of the aerial hyphae with sterile fingernail scissors and subculturing on blood agar slants, incubated at 37°C. Skin tests and complement fixation tests with stock cultures of *Blastomyces* were negative. The fungus from this patient fixed complement with the serum from patient 10.

He was discharged as hopeless two days after his third admission. A letter from his family physician stated that he died during the summer of

1935, a little over four years from the time of onset. Necropsy was not obtained.

Cases 10, 11 and 12 improved satisfactorily with the combination of iodide and vaccine therapy.

Case 10 is of special interest in that this is the only surviving patient in our series who had a high titre of serum antibodies. She was moderately allergic and, after desensitization by vaccine treatment, responded well to iodides. The operative evacuation of the focus in the uterus and tubes was followed by the disappearance of the antibodies, and the subsequent absence of evidence of new lesions suggested that the infection was brought under control. She is still in good health four years after the onset.

Case 10: V. S., no. 40085, a white married woman of 27, was admitted to Duke Hospital on July 8, 1934, complaining of pain in the chest and cough for three months. She was well until March 24, 1934, when she developed a severe attack of kidney colic. Cystoscopy revealed pus but no stones. While recovering from this attack she fell, breaking her left arm and "wrenching" her back, followed for several days by a complete paralysis of both legs. Return of function was rapid, and she was able to walk by the time the arm was healed. The day after the fall she coughed up some bright red blood, had fever of 40°C. (104°F.), and was acutely ill for about two weeks. The cough persisted after the fever subsided, and she developed constant severe pain in the left side of the chest anteriorly. She was admitted to a local sanatorium for study on April 15, 1934. Chest roentgenograms showed a dense pneumonic process in the left upper lobe. The sputum was negative for tubercle bacilli, and she was discharged after a week. The cough became more severe, she lost weight, and the pain in the left chest and left shoulder became more intense. She entered the Pine-Crest Manor Sanatorium on June 26, 1934, where she was studied by Dr. J. W. Dickie. During her ten days' stay in the sanatorium the sputum became more purulent, was frequently blood-streaked, and pain appeared for the first time in the right shoulder. The sputum was negative for tubercle bacilli although the roentgenogram showed an extension of the infection in the left upper lobe. Carcinoma of the lung was suspected, and she was referred to Duke Hospital for bronchoscopy.

Physical examination: Temperature 38°C. (100.4°F.), pulse 90, respiration 18, blood-pressure 128/78. She was well nourished, well developed, and constantly annoyed by a deep hacking cough which was productive of small amounts of mucopurulent blood-streaked sputum. Over the left upper lobe there was dulness, decreased tactile fremitus, increased whispered voice, and bronchial breathing with numerous fine and medium moist râles. A few moist

râles were heard along the right border of the sternum. The mid-dorsal spine showed a slight kyphosis with some tenderness on pressure, but there were no changes in sensory, vibratory or position senses. The deep and superficial reflexes and the plantar responses were normal. There was an unsustained ankle clonus.

Stereoscopic films of the chest showed a dense process radiating outward from both hila (plate 4, figure 14). On the left side the lesion spread outward and upward along the upper lobe bronchi, suggesting malignancy.

Red cells 3,800,000, haemoglobin 10.7 g. (68 per cent), white cells 10,800, polymorphonuclears 73 per cent, eosinophiles 2 per cent, large lymphocytes 8 per cent, small lymphocytes 10 per cent, monocytes 7 per cent. No tubercle bacilli could be found in the sputum, and cultures were negative for fungi. Wassermann negative. Urine normal.

Bronchoscopy by Dr. Watt Eagle showed no evidence of neoplasm, and the pus, aspirated from the left upper lobe through the bronchoscope, contained double-contoured budding organisms resembling *Blastomyces*.

Cultures on blood agar plates incubated at 37°C. gave a good growth of *Blastomyces dermatitidis*. The patient's serum fixed complement in high titre with her own strain and with cultures isolated from cases 1, 5, 6, 9 and 11. A skin test with the *Blastomyces* vaccine prepared from the strain isolated from case 6 gave a 2+ skin reaction after 24 hours.

One-tenth cc. of a 1 to 10 dilution of the skin-testing vaccine was injected subcutaneously without reaction. The dose was increased 0.2 cc. every two days until she was receiving 0.8 cc. of the undiluted vaccine. After being partially densensitized she was given 0.5 cc. t.i.d. of ethyl iodide by inhalation, increasing by 0.25 cc. daily until she was receiving 2 cc. t.i.d. She also was given a saturated solution of potassium iodide, 1 drop t.i.d., which was increased 3 drops daily until she was taking 12 drops t.i.d. From September 4 to 6 she was given three deep X-ray treatments over the left upper lobe front and back. The cough began to diminish in two weeks, and the cough and sputum were practically absent at the end of a month. The fever disappeared by the third week, and her temperature remained normal until the time of discharge. There was marked clearing of the infiltration at the right hilum and an appreciable decrease of the shadow in the left upper lobe. One month after the beginning of the combined iodide and X-ray treatment, the films showed a disappearance of the lesion of the right hilum and a great reduction of the shadows in the left upper lobe (plate 4, figure 15).

On September 10, 1934, while in the hospital, the patient complained of weakness of the legs when walking. The weakness progressed so rapidly that she was unable to walk about the ward. She was upset emotionally, profoundly depressed and complained of aching in the back and legs. On examination the muscles of the legs were tender, and there was a moderate degree of mus-

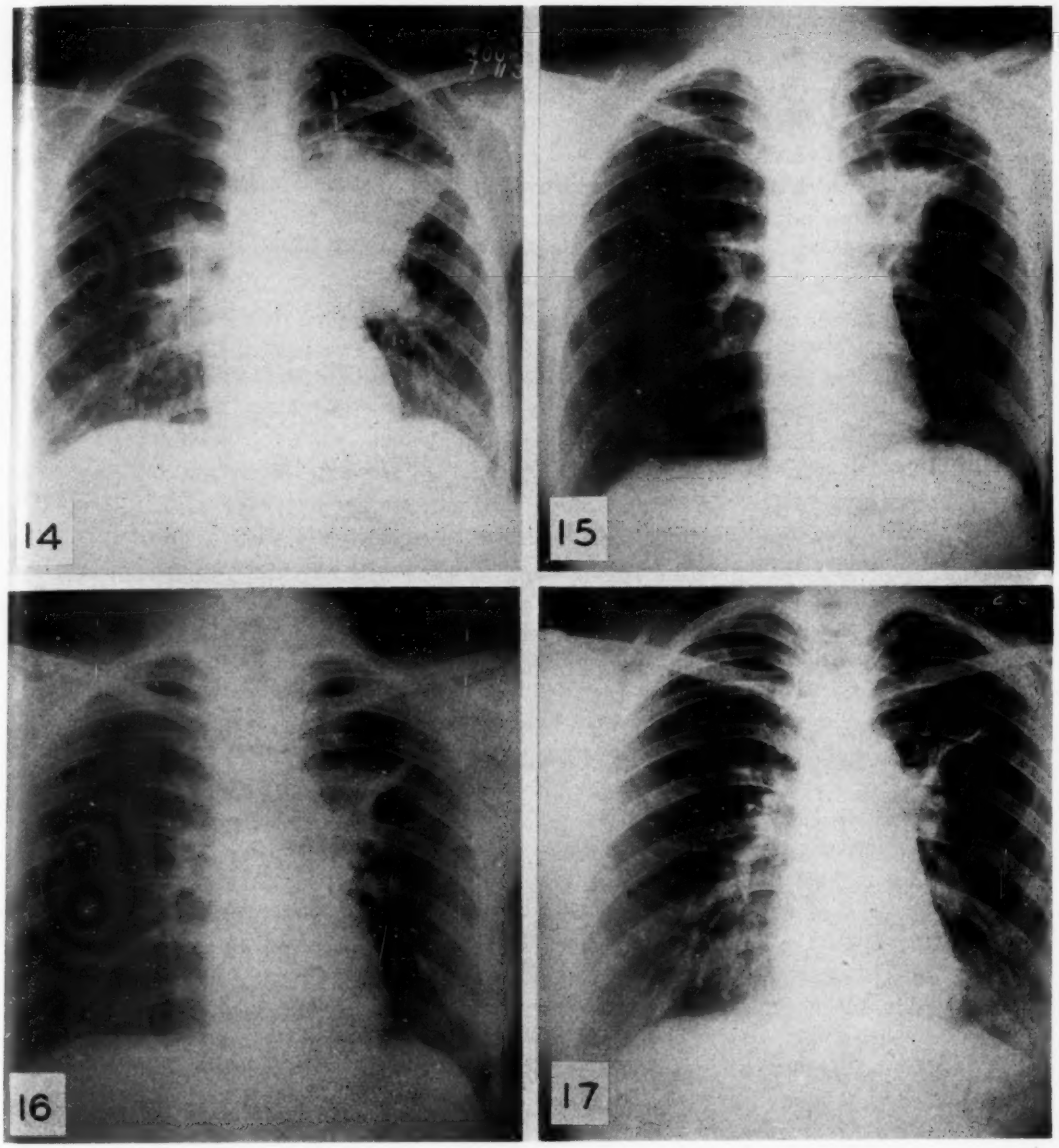


PLATE 4

Healing pulmonary blastomycosis (case 10)

FIG. 14. Appearance of pulmonary lesion July 11, 1934.

FIG. 15. Appearance of lesion August 6, 1934.

FIG. 16. Roentgenogram January 24, 1935.

FIG. 17. Roentgenogram February 3, 1937.

cular weakness. The reflexes were normal or slightly hypoactive, plantar response was normal, and there was no ankle clonus. Iodism was suspected but not confirmed by chemical studies. The spinal fluid was normal. Roentgenograms of the vertebrae showed a partial collapse of the twelfth lumbar vertebra with a reduction of the anterior margin to about one-half its normal width, but no kyphosis or displacement. Lipiodol was injected by cisternal puncture, but roentgenograms showed no evidence of a block at the level of the injured vertebra. We concluded at the time that she probably had a pathological fracture of the vertebra due to blastomycosis. Dr. A. L. Shands, of the Department of Orthopedics, applied a corset and splints and directed the patient to sleep on a fracture board. Neurological examination on October 11, 1934 showed absence of ankle jerks and a loss of vibratory sense on the right side up to the anterior superior spine. She was discharged October 23, 1934 and instructed to rest in bed and return at monthly intervals for orthopedic treatment.

The lungs continued to improve, and a roentgenogram made January 24, 1935 (plate 4, figure 16) showed the disappearance of the dense mass in the left upper lobe, leaving a fairly extensive area of fibrosis. The symptoms in the extremities persisted, and in March, 1935 she began to have irregular menses with excessive blood loss and lower abdominal pain. She was admitted to the Gynecological Service on April 2, 1935. Blastomycetes were seen in smears and sections of uterine curettings, and operation revealed blastomycosis of the uterus and tubes. She made a satisfactory recovery and was discharged April 25, 1935. The details of this gynecological study were reported by Hamblen, Baker and Martin.

Alternating courses of potassium iodide and desensitizing doses of vaccine were continued. The shadows in the chest continued to decrease, but the condition of the legs gradually became worse. She was readmitted on February 7, 1937. Examination by Dr. E. C. Hamblen showed no evidence of recurrence in the pelvic organs. Chest roentgenograms showed almost complete disappearance of the pulmonary lesion (plate 4, figure 17). There was a spastic paraplegia with hyperactive knee jerks, ankle clonus and a positive Babinski, but no sensory changes. Vibratory sense was diminished. Lipiodol injection showed partial obstruction at the level of the twelfth thoracic vertebra. Laminectomy by Dr. Deryl Hart revealed a mass of granulation tissue in the region of the original injury which corresponded to the location of the partial block. Although the operator considered this small mass of tissue inadequate to account for all of her symptoms, the patient maintained that she began to regain control of her legs within a few days. She was discharged from the hospital March 7, 1937 and improved slowly for the next six months, becoming able to walk with crutches and drive a car.

In April, 1935 the complement fixation titre to a mixed *Blastomyces* antigen

showed a titre slightly lower than before, and a test made in December, 1935 was completely negative. Several serological examinations since that time have been entirely negative.

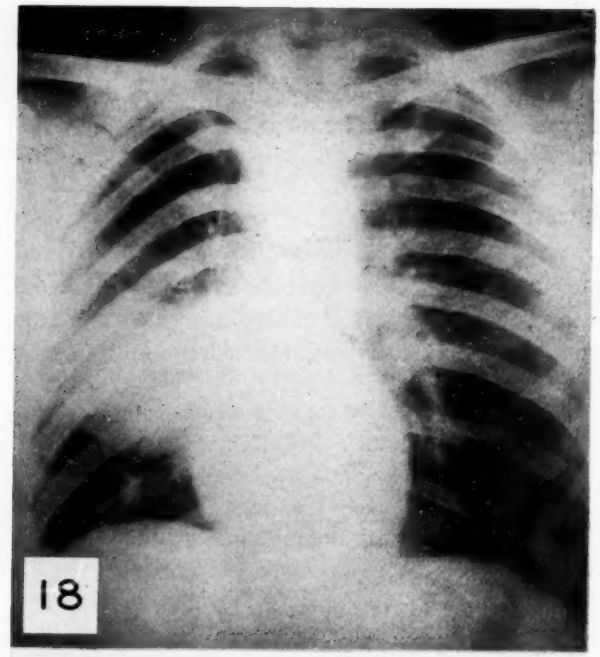
Case 11 illustrates a high degree of allergy without serum antibodies. Injection of desensitizing doses of vaccine followed by iodide therapy resulted in rapid healing of the lesions. The failure to develop serum antibodies after vaccine therapy is offered as evidence that the beneficial effect of the vaccine did not result from active immunization.

Case 11: A. Y., no. 48069, a white male farmer of 34, was admitted to Duke Hospital on January 21, 1935, complaining of a sore on leg for four weeks. He enjoyed excellent health until four years ago, when he developed a nonproductive cough. The stools had contained streaks of blood for the past two years, and he developed nocturia during the past five months. At intervals during the past year there appeared over the legs reddish nodules which had ruptured, drained purulent material, and healed. Four weeks before admission he developed a sudden severe pain in the right leg followed by swelling and redness. The abscess was incised by his family physician, and bloody pus continued to drain until the time of admission.

Physical examination: Temperature 38°C. (100.4°F.), pulse 100, respiration 22, blood-pressure 115/70. He was well developed, poorly nourished, and chronically ill. The skin had three different types of lesions. In the calf of the right leg and in the left buttock were open lesions which were draining sanguinous material. On the upper part of the left shin and upper part of the medial surface of the left arm were two oval fluctuating areas about 2 x 5 cm. which showed no inflammation of the overlying skin but were definitely hot and tender. On the medial surface of the right hand just above the wrist and on the lateral surface of the left foot just anterior to the external malleolus were two elevated, dull red, tender areas 1.5 x 2 cm. which showed no surrounding induration. The cervical and inguinal lymph nodes were slightly enlarged. Over the right lung, posteriorly below the angle of the scapula, extending laterally toward the axilla, there was dulness, bronchial breathing, and fine râles were elicited by expiratory cough.

Chest roentgenograms showed a dense consolidated area with all the characteristics of a pneumonic process, extending from the right hilum to the lateral chest wall in the right middle lobe (plate 5, figure 18). Roentgenograms of the bones showed no evidence of destruction in the regions of the subcutaneous abscesses.

Red cells 3,450,000, haemoglobin 11.7 g. (75 per cent), white cells 16,600, polymorphonuclears 88 per cent, eosinophiles 2 per cent, basophiles 1 per cent, large lymphocytes 1 per cent, small lymphocytes 7 per cent, monocytes 1 per



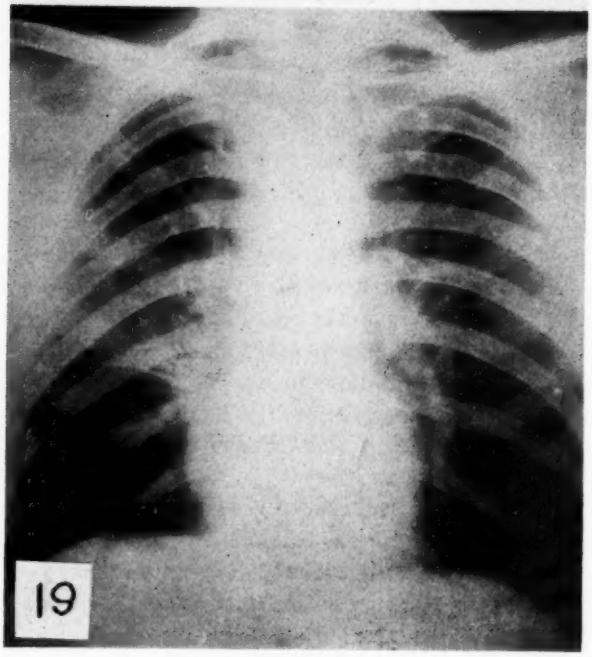


PLATE 5

Healing pulmonary blastomycosis (case 11)

FIG. 18. Appearance of pulmonary lesion January 21, 1935.

FIG. 19. Appearance of lesion April 12, 1935.

cent. Sedimentation rate moderately increased. Wassermann and Kahn reactions negative. Urine normal.

Smears of the bloody material from the lesion on the buttock showed budding fungi, and cultures on blood agar at 37°C. and Sabouraud's media at room temperature were positive for *Blastomyces dermatitidis*. Skin test with a vaccine made from the homologous culture gave a reaction comparable to a 4+ tuberculin reaction with sterile abscess formation. The patient's serum failed to fix complement with several cultures of *Blastomyces* including the homologous strain.

The open skin lesions were treated with dressings soaked in a saturated solution of potassium iodide. An attempt was made to desensitize the patient by giving gradually increasing doses of *Blastomyces* vaccine subcutaneously, beginning with 0.5 cc. of a 1 to 1000 dilution of the vaccine used for skin test. The dose was increased by 0.25 cc. every second day until he was receiving 1 cc. of a 1 to 100 dilution. Skin tests at the time of discharge showed only a slight reaction. After he was fairly well desensitized, potassium iodide was given by mouth, beginning with 3 drops of a saturated solution t.i.d. and increasing 3 drops daily until he was receiving 20 drops t.i.d. During the vaccine treatment and prior to the iodide therapy there was a marked improvement in the skin lesions. The open ulcers began to heal rapidly, and the subcutaneous abscesses, after draining spontaneously, healed promptly. There was a remarkable clearing in the chest roentgenogram, about three-fourths of the infiltration disappearing in ten days. His general condition and appetite improved, he was afebrile during the last two weeks of hospital treatment, and he gained 15 pounds in weight. He was discharged March 10, 1935, six weeks after admission, with instructions to continue taking 20 drops of potassium iodide t.i.d. after meals.

He returned for reëxamination one month later. He felt well and all his lesions had healed except one, which still drained a small amount. A chest roentgenogram (plate 5, figure 19) showed complete clearing of the infiltration in the right lung, leaving a few residual strands of fibrosis. He was instructed to continue the potassium iodide therapy.

On May 15, 1936, one year later, the patient reported that he had no more skin or subcutaneous lesions and no return of cough or night sweats. His weight was 154 pounds, a gain of 16 pounds after leaving the hospital. Recent letters to the patient have been returned undelivered, and we have been unable to learn of his present condition.

Case 12 illustrates the harmful effect of iodides on the skin lesions of a markedly allergic patient. Fever, loss of weight and extensive spread of the lesions occurred after iodide administration, and improvement resulted only after the iodides were stopped and vaccine therapy instituted.

Case 12: H. L., no. 68019, a male Negro of 33, was admitted to Duke Hospital on June 19, 1936, complaining of sores on buttock for ten months. Past history was uneventful except for hard chancre at 16, gonorrhoea at 19, and a soft chancre at 21 years of age. The present illness began ten months prior to admission with intense itching about the anus, followed in two weeks by an ulcer which discharged thick white pus. The ulcer spread to involve the entire perineum, causing painful defaecation. Several similar but smaller lesions then appeared on both buttocks.

Physical examination: Temperature 37°C. (98.6°F.), pulse 80, respiration 20, blood-pressure 145/100. He was well nourished, well developed, and did not appear ill. There was a raw, ulcerated, fungating lesion with irregular elevated borders covering the entire perineum from just below the tip of the coccyx to the posterior base of the scrotum. The anal opening was small, scarred, and deformed so much that the examining finger could enter the rectum only at an angle. Several shallow ulcers, from 3 to 4 cm. in diameter, with raised edges were present over both buttocks. The inguinal lymph nodes were enlarged. The lungs were clear except for a few scattered râles. The heart was normal.

Roentgenograms showed no evidence of pulmonary disease.

Red cells 3,820,000, haemoglobin 10.5 g. (68 per cent), white cells 7,120, polymorphonuclears 85 per cent, large lymphocytes 1 per cent, small lymphocytes 12 per cent, monocytes 2 per cent. Wassermann and Kahn reactions negative. Urine normal.

Blastomycetes were seen in smears and in biopsy sections. *Blastomyces dermatitidis* was isolated after seven days' incubation on blood agar at 37°C. and Sabouraud's medium at room temperature. Skin test with the standard *Blastomyces* vaccine was strongly positive. Complement fixation tests with stock cultures and the homologous strain were repeatedly negative.

Treatment with potassium iodide was started June 23, 1936. He received 1 cc. of a saturated solution the first day, and this was increased by 0.3 cc. increments until he was receiving 9 cc. each day. After two weeks' treatment he complained of feeling worse. His temperature, which had been normal, began to fluctuate between 37.2°C. and 39.6°C. (99°F. and 103°F.) (figure 3). The pulse rate had also increased, varying from 100 to 130. The lesions on the buttock spread rapidly, and the tissues about the rectum liquefied, discharging increasing amounts of thick white pus. It was no longer possible to do a rectal examination since the supporting structures were destroyed, and the rectum disappeared into the pelvis when pressure was applied with the finger. He lost 4.9 kilograms (10.8 pounds) in weight during the three weeks of treatment. The potassium iodide was discontinued ten days after the appearance of fever when it was evident that the drug was spreading the infection. He was then treated by injections of heat-killed *Blastomyces* vac-

cine, beginning with 0.1 cc. of a 1 to 10,000 dilution of the stock vaccine, and rapidly increasing by 0.3 to 0.5 cc. increments every other day until he was taking 0.5 cc. of a 1 to 100 dilution. He felt better in a few days, and the temperature was normal within six days. The lesions began to heal, and he gained 4 kilograms (9.8 pounds) in the next three weeks.

The patient was discharged August 18, 1936, two months after admission, with instructions to return to the out-patient department for continued vaccine treatment and periodic dilatations of the rectum.

The vaccine treatment was continued until he was receiving 0.5 cc. of the undiluted vaccine without reaction. Potassium iodide again was given in small doses. The lesions on the buttock healed satisfactorily. In spite of periodic dilatations of the rectum, scarring became so excessive that the rectum would no longer admit the examining finger, and he was readmitted to the hospital on January 18, 1937 for excision of the scarred area. Dr. Samuel Upchurch, of the Department of Surgery, excised two large polyps and the base of the old ulcer which surrounded the anus. No blastomycetes were found in this tissue by smear, microscopical section or culture. Pinch grafts on the denuded area were unsuccessful. Eighteen hundred roentgen units of X-ray were given over the rectal area from March 1 to March 6, 1937. He also received antisyphilitic treatment and was discharged March 6, 1937.

Although his blastomycosis was apparently cured, he was hospitalized from October 11, 1937 to November 28, 1937 for treatment of his perianal ulcer. He improved markedly with potassium permanganate (1 to 4000) compresses and 2 per cent scarlet red ointment. Pinch grafts were applied October 29, 1937, and after treatment with cod liver oil ointment, epithelization had progressed so well that he was discharged November 28, 1937.

Case 13 is of interest in that it was possible to study the state of allergy to the protein and carbohydrate fractions of the fungus. Partial desensitization was accomplished by the intravenous injection of the carbohydrate fractions.

Case 13: N. A., no. 78322, a Negro male laborer of 25, was admitted to Duke Hospital on December 29, 1936, complaining of sores on right foot and left ankle for three years. The patient had a penile lesion ten years before admission and was given one intramuscular injection of some unidentified drug. In 1933, after his Wassermann was found to be positive, he received six intravenous and two intramuscular injections in the course of five weeks. In the fall of 1933, while the inmate of a prison camp, he had night sweats and developed a chronic cough productive of green, blood-streaked sputum, but no evidence of tuberculosis was found by the prison doctor. The patient then noted a swelling on the left thumb which drained a thin watery fluid and

healed in a month. During this interval a similar lesion appeared on the left buttock which also healed after spontaneous drainage. Two months later a mass appeared on the right heel which broke through to the surface after several weeks and did not heal. The fungating granulations progressed until they covered the heel and encircled the ankle and lower third of the leg. One month after the beginning of the latter lesion, a mass appeared on the left shoulder which became an open ulcer with fungating granulations which extended over the entire shoulder. Three weeks before admission a mass appeared in the left inguinal region, and one week later similar masses were noted in the right groin and upper third of the right leg. The lesion in the left groin ruptured and drained a grayish white exudate.

Physical examination: Temperature 37°C. (98.6°F.), pulse 80, respiration 20, blood-pressure 130/70. The patient was undernourished, well developed, and did not appear acutely ill. The anterior and superior aspects of the left shoulder were covered by a large shallow ulcer with a rolled indurated edge. The base was fiery red and spotted with small warty projections which exuded thin, foul-smelling pus. A similar ulcer encircled the right ankle, extending up the inner side of the leg for about one-third of the distance to the knee. There was a healed scar in the left inguinal region and fluctuant abscesses in the region of the upper third of the right tibial and right inguinal regions.

Chest roentgenograms showed moderate peribronchial thickening with some small tracheobronchial lymph nodes, suggesting chronic upper respiratory infection.

Red cells 4,250,000, haemoglobin 12 g. (77 per cent), white cells 16,750, polymorphonuclears 79 per cent, basophiles 1 per cent, large lymphocytes 4 per cent, small lymphocytes 14 per cent, monocytes 2 per cent. Wassermann negative, Kahn 1+ on two occasions. Urine and stool negative.

The abscesses in the right leg were incised and drained. Double-contoured budding forms were seen in smears and biopsies, and *Blastomyces dermatitidis* was grown from all lesions. Complement fixation tests were negative. He gave positive delayed reactions to intracutaneous injections of the heat-killed vaccine and the carbohydrate fraction derived from the strain originally isolated from case 5.

He received two intramuscular injections of bismuth and four intravenous injections of neoarsphenamine while in the hospital. The open ulcers were treated with compresses saturated with 1 per cent copper sulphate solution, and he also received, at intervals, five treatments with the same solution by iontophoresis. Desensitization was attempted by intravenous injections of the carbohydrate fraction of *Blastomyces dermatitidis*. He received 0.000,03 g. the first day, and this was increased by approximately 0.000,1 g. every third day until he reached a maximum of 0.004 g. A skin test after this treatment showed reduction in sensitivity to the carbohydrate fraction and a markedly

reduced reaction to the heat-killed vaccine. He was then given potassium iodide by mouth, 0.3 cc. t.i.d. which was increased by 0.1 cc. t.i.d.

The patient was discharged February 22, 1937 with instructions to continue treatment in the out-patient clinic, but he failed to return.

SUMMARY AND CONCLUSIONS

From a study of the recorded cases of blastomycosis and our own series of 13 cases, we have drawn the following conclusions:

American blastomycosis (Gilchrist's disease) is a distinct clinical entity caused by a specific aetiological agent, *Blastomyces dermatitidis*.

Two clinical types of infection are recognized: (*a*) cutaneous blastomycosis, which proceeds as a chronic or subacute ulcerating process and which usually responds to treatment with iodides or radiation, and (*b*) systemic blastomycosis, a highly fatal disease, characterized by pulmonary infection and wide-spread distribution of lesions in the subcutaneous tissues, bones, joints, central nervous system and internal organs.

The same fungus, *Blastomyces dermatitidis*, causes both types of infection.

The disease is far more common in males, and the natural habitat of the fungus is evidently in nature, although proof of its existence in the environment has not been found.

Antibodies can be found in the sera of patients who are heavily infected; they persist until death unless the infectious process is overcome or greatly reduced.

Some patients develop a condition of hypersensitiveness to the infecting fungus, and this allergic state diminishes in the terminal stages of the disease. The degree of hypersensitiveness can be estimated by skin tests and can be materially reduced by the repeated injections of minute doses of a heat-killed vaccine.

Potassium iodide is curative in some cases, but it is a dangerous drug to administer to patients who are allergic to the fungus.

In systemic blastomycosis iodide therapy should be started only after the state of hypersensitiveness has been excluded by skin test or artificially reduced by therapeutic injections of vaccine.

THE ROENTGENOLOGICAL ANATOMY OF THE CHEST[1,2]

II. The Bronchial Distribution

CARLETON B. PEIRCE[3] AND BRUCE W. STOCKING[4]

With the rapid advances in technical procedures for treatment of intrathoracic conditions, it becomes necessary to have a terminology for the bronchi which is particularly apt anatomically, terse and useful for the bronchoscopist, surgeon, clinician, internist and radiologist in mutual consideration of a case. A nomenclature which is graphic and readily understood should be based preferably upon functional anatomy rather than comparative anatomy.

The wide variety of tissues contained within the thorax, and the ready response of the several portions of the lungs to adapt themselves to pathological changes, oftentimes masks an abnormal area by enclosure within a comparatively normal area of lung tissue whose volume may have been increased as a compensatory measure. The diagnosis of the location of a given lesion, the management of treatment and some prognosis as to the direction of spread may be accomplished more successfully, if the clinician and the radiologist have in mind a rather clear picture of the distribution of the bronchial tree and the associated vascular structures within the chest.

Significant variation from the usual pattern of the lobar structure of the lung and its associated bronchial distribution rarely occurs. The most common variant is due to the azygos vein on the right creating a fourth lobe on that side. An occasional accessory pleural fissure in the posterior inferior lung base on either side may produce an apparent accessory lobe. Upon the left side, the lingular portion of the superior lobe, which includes the inferior third of the superior lobe extending from the third anterior rib to the diaphragm (a much larger volume than

[1] Presented at a session of the Pathological Section at the 34th annual meeting of the National Tuberculosis Association, Los Angeles, California, June 22, 1938.

[2] The invaluable assistance rendered by Professors Alexander, Patten, McCotter and Barnwell and Doctors Woodburne and Curtzwiler of the University of Michigan Medical School is gratefully acknowledged.

[3] Royal Victoria Hospital, Montreal, Quebec.

[4] Foote Memorial Hospital, Jackson, Michigan.

the classical anatomical *lingula pulmonalis*) may be separated by an accessory fissure as is the case of its analogue, the right middle lobe. But the pattern of the bronchial distribution, and hence of the pulmonary artery, is maintained without appreciable variation. These accessory lobes are merely divisions by accident of development, which in fact accentuate the constancy of the bronchial distribution and its associated lobular arrangement of the lung parenchyma, rather than alter it.

The researches of Aeby, Ewart, Huntington, Hasse and others have furnished much information on the comparative anatomy and detailed morphology of the bronchial distribution. Miller's recent monograph has clarified the knowledge of the fundamental structure of the lungs. But the roentgenologist, dealing with the shadow density cast by pulmonary disease, finds himself lost in the bulky classical terminology by which he must convey to his colleagues his visual impression of the distribution of the bronchi and pulmonary vessels in relation to a given lesion.

The relationship of the trachea and major bronchi to the cardiovascular structures has given rise to the use of the terms *eparterial* and *hyparterial*. But designation of their branches as *dorsal* or *ventral hyparterial I*, *II* or *III*, etc. does not indicate graphically the areas of pulmonary tissue which they individually supply.

The relative symmetry in distribution of the lesser bronchi seems to us to emphasize the propriety of a somewhat similar terminology in the two lungs (figure 1). The retention of the qualifying adjective "main" or "major" in reference to the primary bronchi is superfluous, and the occurrence of a left eparterial bronchus is so rare that *hyparterial* has little significance on that side. The constancy of the eparterial position of the bronchus for the right superior lobe suggests that the use of hyparterial as a qualification of a superior lobe bronchus, which could be so situated, would be the more important. Except for the origin of the right superior bronchus, the distribution of the bronchi is three-directional more often than two-directional in the transverse plane. Bronchographically, each succeeding group of smaller branches is virtually of equal calibre and of practically simultaneous origin from the parent bronchus, directed radially toward the respective parenchymal segments.

Right lung: Although in a certain sense one might consider the *right bronchus* (*Stammbronchus*) as extending from the *carina* to the origin of

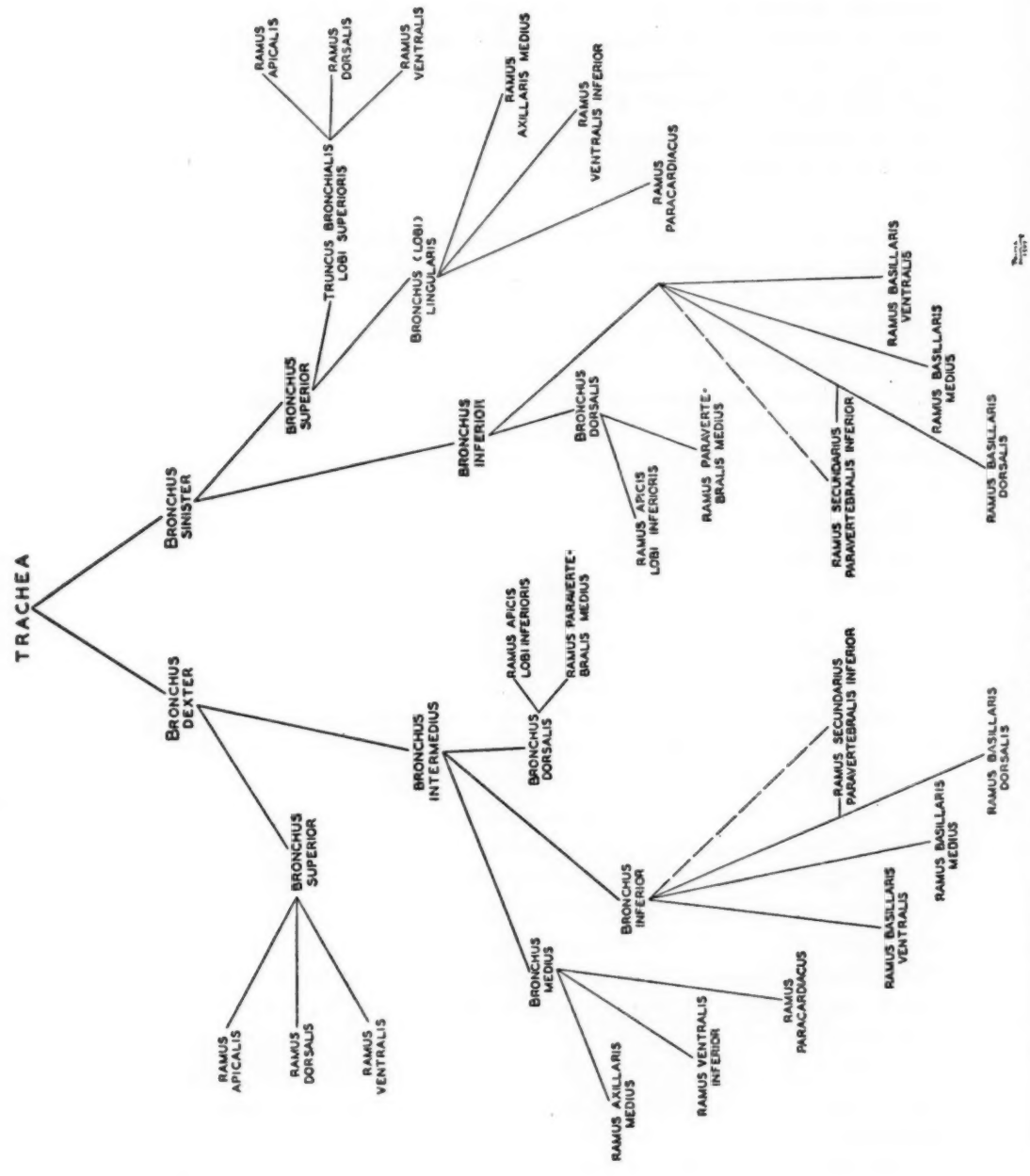


FIG. 1. Schema of the trachea and bronchi

the middle lobe bronchus, we prefer to consider the *right bronchus* as only that short segment intervening between the *carina tracheae* and the origin of the eparterial or *superior bronchus*.

The segment which extends between the superior bronchus and the tripartite division at the level of the origin of the middle lobe bronchus preferably should be designated as the *intermediate bronchus* (Ewart, Twining). This tripartite division produces (*1*) the *middle* (lobe) *bronchus*, (*2*) the *dorsal bronchus* (supplying the apex of the inferior lobe) and (*3*) for the remainder of the inferior lobe the *inferior bronchus*, which then divides into *ventral basilar*, *median basilar* and *dorsal basilar rami*, each ramifying further (and in a similar manner) to supply rather constant segments of the inferior lobe. The *inferior paravertebral ramus* may be a secondary branch of the dorsal basilar ramus, or may arise as a fourth branch of the inferior bronchus.

Similar tripartite divisions of the eparterial or *superior bronchus* and of the *middle bronchus* are the rule. The *superior bronchus* commonly divides into *dorsal*, *apical* and *ventral* rami; the *middle bronchus* into *midaxillary*, *inferior ventral* and ventro-mesial or *paracardiac* rami.

Left lung: There is no good reason to consider the *left bronchus* (Stammbronchus) as extending beyond its division into two rami, one of which supplies the superior lobe, the other the inferior lobe. This is particularly true if the lingular portion of the left superior lobe is to be considered the analogue of the middle lobe on the right. The calibre of the left *superior bronchus* is commonly equivalent to that of the *inferior bronchus*. There is normally no part of the left bronchial tree similar to the intermediate bronchus of the right lung.

The left inferior bronchus gives off the *dorsal bronchus* for the apex of the inferior lobe, and then almost immediately divides into *dorsal basilar*, *median basilar* and *ventral basilar rami* as on the right side. The bronchus for the left *inferior paravertebral* area is commonly the first off-shoot of the dorsal basilar ramus.

As the left superior bronchus passes the left margin of the bifurcation of the pulmonary artery, it curves slightly cephalad, dividing almost immediately into a *superior trunk*, (Twining[5] has suggested the term *apico-pectoral bronchus*) from which arise *dorsal*, *apical* and *ventral rami* as on the right side, and a ventro-lateral descending trunk, the *lingular bronchus*, which supplies that portion of the superior lobe below the third rib anteriorly, between the pericardial pleura mesially and the interlobar

[5] E. B. Twining, Manchester, England. Personal communication.

FIG. 1. Schema of the trachea and bronchi

fissure laterally, and consequently includes the *lingula pulmonalis* (B. N. A.). This *lingular bronchus* divides into three rami very similar to those of the middle bronchus on the right; namely, an *inferior ventral*, a *midaxillary* or *lateral* and a *paracardiac*. We have found but one instance in which the lingular bronchus arose independently of the superior bronchus.

We believe the dignity of recognition as a major entity in the pulmonary system should be given to this inferior third of the left superior lobe, which occasionally presents a partial pleural incisura, but rarely an independent origin of its bronchus. It commonly is involved as an entity separate from the remainder of the superior lobe, and in association with lesions of the inferior lobe. As a corollary, the portion of the left superior lobe supplied by the superior trunk is not uncommonly involved in disease independent of the lingula. Such pathological behavior by these portions of the superior lobe may be considered as indicative of their normal functional anatomic relationship. A similar relationship is often encountered in the pathological changes of bronchiectasis and pneumonia in the right middle and inferior lobes on the right. The normal respiratory functional changes of the *lingular lobe* comparable to the right middle lobe were observed, we believe, in the studies by Hudson and Jarre, although not interpreted as such in their discussion of the angles of divergence of the lower bronchi.

The normal superimposition of the several pulmonary lobes in the anteroposterior axis produces a complex bronchial mosaic in the frontal roentgenogram (figures 2a and 2b). Studies of the bronchial tree and lung fields in the frontal plane, stereoscopically, and in the lateral projection often do not afford the degree of visualization which is possible in the oblique projection.

For bronchography, we have found stereoscopic oblique projections often preferable to the usual routine frontal and lateral studies, as discussed in a previous paper.[6]

The *right anterior oblique projection* affords the maximum visibility of the posterior right lung field. In bronchography it displays the left bronchial tree to a maximum advantage. The right superior lobe is so projected that it occupies the major portion of the upper diagonal half of the chest, overlying the trachea and great vessels to below the level of the carina. The middle lobe overlies the right half of the heart shadow in apposition to the right atrium. The posterolateral portions

[6] Am. J. Roentgenol. & Rad. Therapy, 1937, *38*, 245.

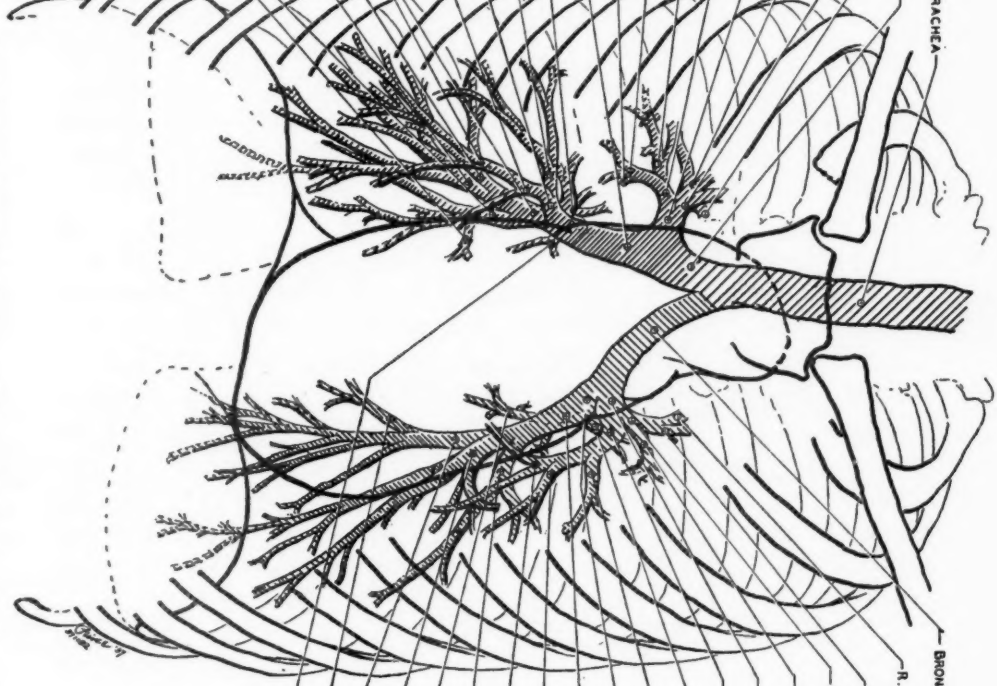


FIG. 2a. Line drawing from bronchogram. The bronchial tree in frontal projection

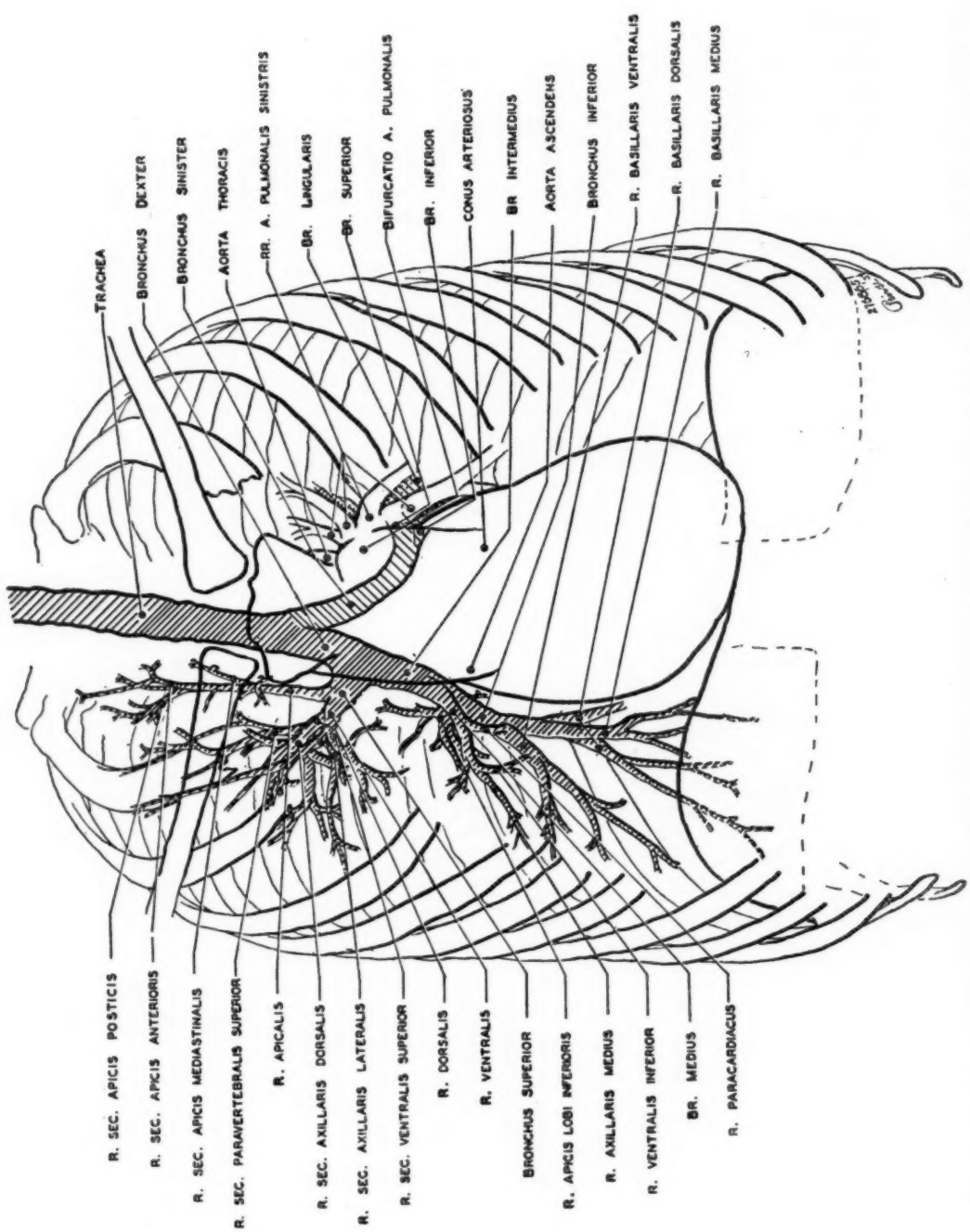


FIG. 2b. Line drawing from bronchogram. The right bronchial tree in frontal projection showing the branching of the superior bronchus

of the left lung are overlaid by the mediastinum, great vessels and heart; however, the anterolateral segment, especially the lingula, is well visualized. The posterolateral right and the anterolateral left costophrenic sinuses are visualized best in this plane.

The trachea in this projection (figure 3) courses downward slightly to the right of the midline to divide at the level of the fifth or sixth thoracic vertebra. The aortic impression on the trachea normally is evident. The left bronchus extends downward, ventralward and to the left, passing postero-inferior to the left pulmonary artery, to divide into the superior and the inferior left bronchi at the lateral margin of the bifurcation of the pulmonary artery. In the anatomical or frontal plane, the left bronchus and its major branches divide and course predominantly within a narrow area near the sagittal axis. But the oblique projection displays these bronchi in a plane at right angles to the roentgen beam, which affords a far better visibility of the entire left bronchial tree.

At this angle the major cardiovascular shadow is produced by the superimposed right and left atria on the right, and the superimposed ventricles on the left. The superior portion of the left cardiac mass is a projection of the pulmonary artery in profile. The right pulmonary artery (obscured by the descending aorta in the frontal projection) and the right pulmonary veins may be brought into view. The ascending aorta will overlie the descending aorta, with the horizontal portion of the arch commonly in optical section. The innominate, left common carotid and left subclavian arteries are projected to the left of the trachea, the superior vena cava overlying the trachea but not readily visualized by means of any intrinsic differential density.

The *left anterior oblique projection* affords the maximum visibility of the left lung field and the right bronchial tree. The left superior lobe is projected to the right of the midline overlying the arch of the aorta, the great vessels, trachea and primary bronchi. The lingular portion overlies the pulmonary conus, the right ventricle and in some extent the left ventricular apex. The right anterolateral and the left posterolateral costophrenic sinuses are best visualized in this projection.

In the left anterior oblique view (figure 4), the trachea occupies the midline, passing between the "fork" formed by the innominate artery and the superior vena cava on the right and the common carotid and the subclavian arteries on the left. The arc of the trachea, as it passes posterior and to the right of the horizontal portion of the aortic arch,

FIG. 2b. Line drawing from bronchogram. The right bronchial tree in frontal projection showing the branching of the superior bronchus

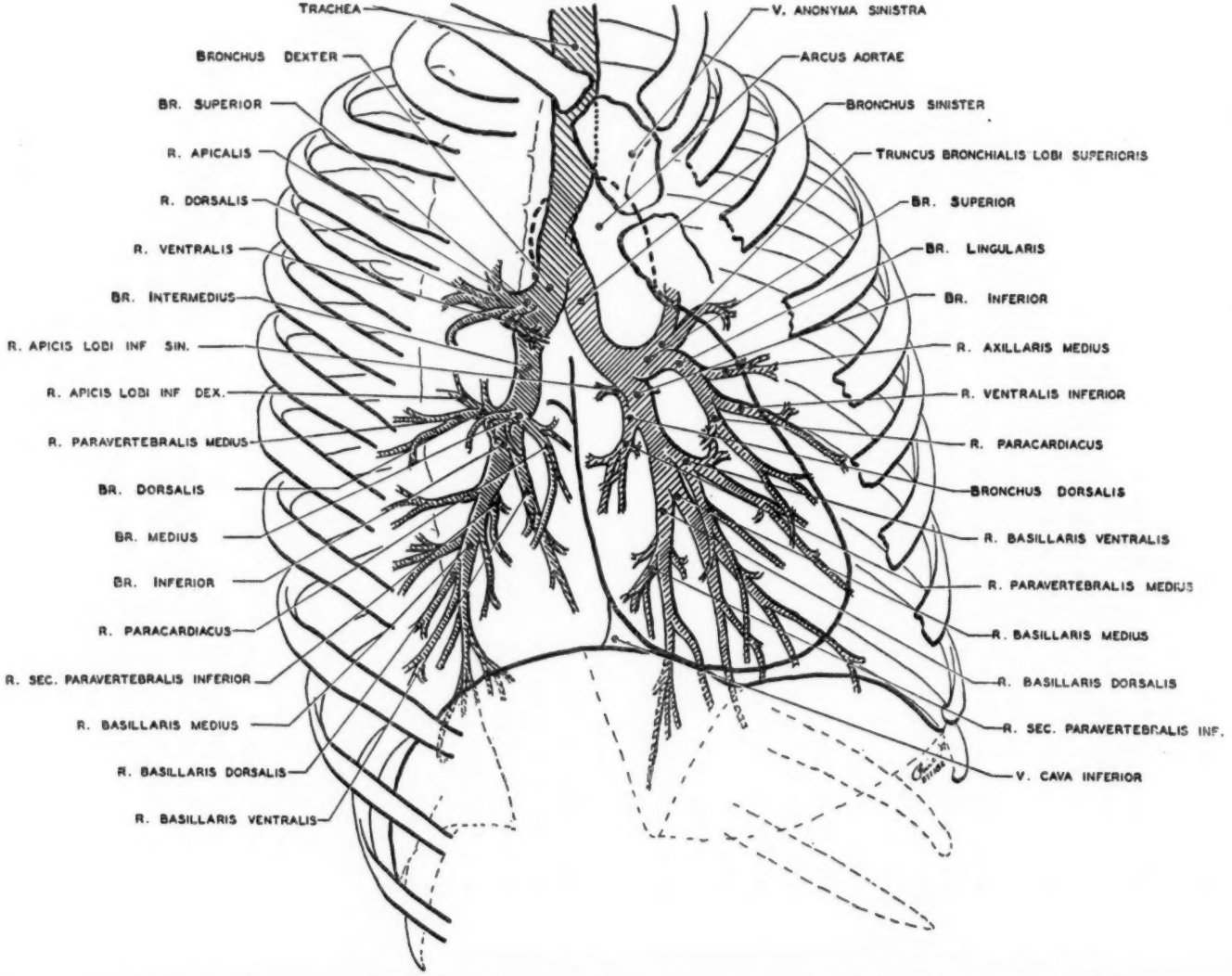


FIG. 3. The bronchial tree in right anterior oblique projection (for demonstration of the left bronchus and its branches)

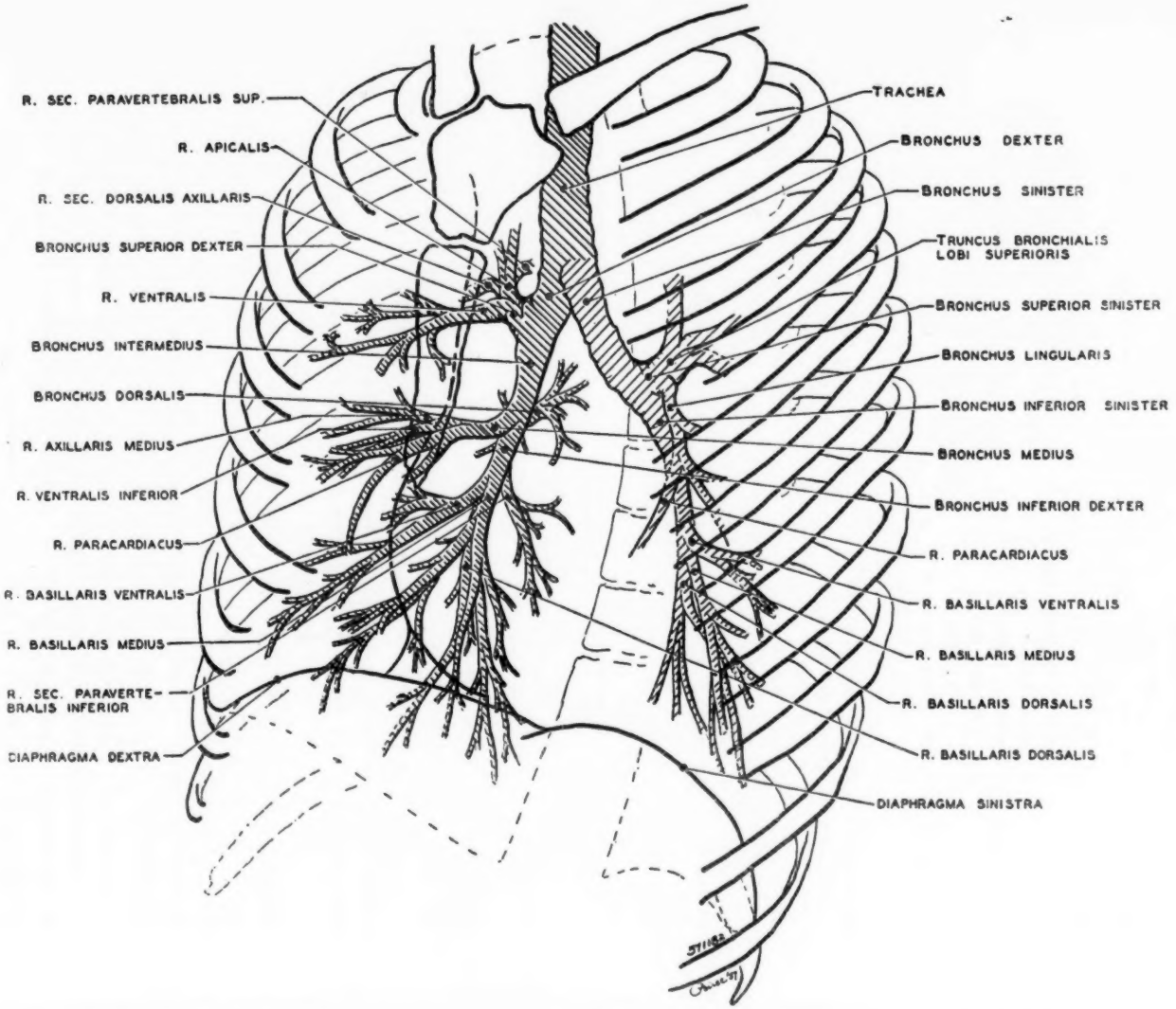


FIG. 4. The bronchial tree in left anterior oblique projection (for demonstration of the right bronchus and its branches).

FIG. 3. The bronchial tree in right anterior oblique projection (for demonstration of the left bronchus and its branches)

is accentuated. The left bronchus overlies the right slightly, immediately below the *carina tracheae*. The right bronchial tree is visualized to better advantage in this plane for reasons similar to those stated above in regard to the left in the right anterior oblique projection.

As has been shown repeatedly in the literature since the advent of roentgenology, the left anterior oblique projection affords the maximum individual visibility of the right ventricle, the left chambers of the heart and the aortic arch. In this plane the interventricular septum is superimposed upon the interatrial septum. The branches of the aortic arch are separated to the maximum. The distribution of the left pulmonary artery is at its maximum visibility.

Technically we believe the bronchographic study of one entire lung at one examination, and of the contralateral lung at a second, is preferable to the injection of a portion of either or both at one time.

In summary, we submit for consideration a terminology for the bronchi which we believe is more useful than the older nomenclature, with which it is compared.

New	*Old*
I. Right bronchus	I. Bronchus dexter
A. Superior bronchus	A. Bronchus dexter eparterialis
B. Intermediate bronchus	B. Bronchus dexter hyparterialis
1. middle lobe bronchus	1. ramus bronchialis hyparterialis ventralis I
2. dorsal bronchus	2. ramus bronchialis hyparterialis dorsalis I
3. inferior bronchus	3. bronchus dexter hyparterialis
(a) dorsal-basilar bronchus	(a) ramus bronchialis hyparterialis dorsalis II
(b) median-basilar bronchus	(b) bronchus dexter hyparterialis
(c) ventral-basilar bronchus	(c) ramus bronchialis hyparterialis ventralis II
II. Left bronchus	II. Bronchus sinister
A. Superior bronchus	A. ramus bronchialis hyparterialis ventralis I
1. superior trunk	1. ramus dorsalis bronchis
2. lingular bronchus	2. ramus ventralis bronchis hyparterialis ventralis I
B. Inferior bronchus	B. Bronchus sinister
1. dorsal bronchus	1. ramus bronchialis hyparterialis dorsalis I
2. dorsal-basilar bronchus	2. ramus bronchialis hyparterialis dorsalis II
3. median-basilar bronchus	3. bronchus sinister
4. ventral-basilar bronchus	4. ramus bronchialis hyparterialis ventralis II

BIBLIOGRAPHY

(1) HUNTINGTON, G. S.: Am. J. Anat., 1920, *27*, 99.
(2) HASSE: See WESTERMARK NILS, Acta radiol., 1935, *16*, 531.
(3) LAUBRY, C., COTTENOT, P., ROUTIER, D., AND HEIM DE BALSAC, R.: J. de radiol. et d'electrol., 1935, *19*, 193, 561, 700; 1936, *20*, 65.
(4) LAUBRY, C., COTTENOT, P., ROUTIER, D., AND HEIM DE BALSAC, R.: Presse méd., 1935, *43*, 2071.
(5) GRANDGÉRARD, R.: Arch. d'électric. méd., 1937, *45*, 187.
(6) GRANDGÉRARD, R., AND HEIM DE BALSAC, R.: Presse méd., 1937, *45*, 444.
(7) MILLER, W. S.: The lung, C. C. Thomas, Springfield, Ill., 1936.
(8) EWART, W.: The bronchi & pulmonary vessels, J. & H. Churchill, London, 1889.

PNEUMOPERITONEUM IN THE TREATMENT OF PULMONARY TUBERCULOSIS[1]

Local Effects on the Peritoneum

HAROLD GUYON TRIMBLE, J. LLOYD EATON AND GERTRUDE MOORE

As early as 1930, Overholt (1) showed by his experiments on dogs that pneumoperitoneum caused an elevation of the diaphragms with limitation of motion, but it was not until 1933 that Vajda (2) applied this method to the treatment of two cases of pulmonary tuberculosis. In 1934 Banyai (3) reported his observations on nine cases, and in 1936 Trimble and Wardrip (4) reported eighty cases. Since then pneumoperitoneum has been recognized (5) as a valuable addition to the various methods of collapse therapy available for the treatment of pulmonary tuberculosis.

During the years 1934–1937 we have used this treatment on 152 patients in the tuberculosis wards of the Alameda County Institutions with distinct benefit in many instances. A definite rise in the diaphragm can be obtained and, even more significant, a marked splinting occurs. When associated with an operation on the phrenic nerve, a marked rise of the paralyzed hemidiaphragm, at times to the level of the second rib anteriorly, often results. The value of this procedure is especially apparent in that large group of patients in which pneumothorax has failed (either because of inability to find any free pleural space or because only a small ineffective collapse could be obtained) and in which for various reasons more drastic types of collapse therapy are not indicated at the time. A phrenic crushing plus pneumoperitoneum is often the next logical step in treatment. This may bring the disease to a point where surgery is possible, or may even bring about an arrest. Pneumoperitoneum is indicated in another large group of patients with pulmonary tuberculosis having extensive far advanced bilateral lesions still in the exudative stage, in which no other form of collapse therapy is advisable.

The effects of the rise of the diaphragm on respiration have been interesting. In the absence of chronic myocardial disease, there has

[1] From the Alameda County Institutions, Oakland, California.

been little or no shortness of breath. In fact, in cases complicated by a compensatory emphysema the effect is often beneficial and respirations are facilitated. We have used pneumoperitoneum with improvement in a few cases of pulmonary emphysema uncomplicated by tuberculosis. The work of Kountz and Alexander (6) and Gordon (7) on the use of abdominal binders in the treatment of emphysema makes clear the rationale of this therapeutic effect.

Although there is an extensive literature on the effects of oxygen used as a treatment for tuberculous peritonitis, we have seen no reports on the effects of air on the normal peritoneum, and there has been considerable question regarding the possible after-effects of such long continued therapy.

From clinical observations, the local effects of air in the peritoneal cavity have seemed quite benign and can be compared favorably with the local effects of air in the pleural cavity during pneumothorax therapy. After the first several refills, very few of the patients have experienced any discomfort. Gastrointestinal symptoms have not been of great moment. Occasionally, ascites has been observed, which may come and go, and, except in the presence of a tuberculous peritonitis, has needed no treatment. There is a striking similarity in the behavior of this fluid to the pleural effusions so often noted during pneumothorax. Tuberculous peritonitis has not occurred more often than the normal expectancy. In a few cases an adhesive peritonitis has developed which has made it impossible to continue the refills, again paralleling the adhesive pleuritis that at times develops during pneumothorax therapy.

To determine more specifically the effect of long continued air and pressure on the peritoneum and abdominal viscera, we have studied the autoptic and microscopical findings on 20 patients treated by pneumoperitoneum.

In general, this group of 20 patients was typical of the patients who have far advanced tuberculosis on entering the tuberculosis wards of the Alameda County Institutions. All had a National Tuberculosis Association classification of far advanced pulmonary tuberculosis, and all but one had bilateral disease. The prognosis was considered as unfavorable in all cases. A third of the group had extrapulmonary tuberculous complications and one case was complicated by syphilis. The group included 2 Japanese, 2 Negroes and 5 Mexicans. Ages varied from fifteen to fifty-nine years, 2 being under twenty and 4 over fifty years of age.

The cause of death was advancing pulmonary tuberculosis in 15 cases, 9 of these complicated by gastrointestinal tuberculosis and 2 by tuberculous peritonitis; in 2 cases the immediate cause of death was severe pulmonary haemorrhage. Improvement was noted at some period during pneumoperitoneum therapy in several cases, and 4 improved sufficiently to have pneumoperitoneum discontinued in favor of major surgery; wax apicolysis in 3 and thoracoplasty in one. In these, death was due to cardiac decompensation in 2, acute dilatation of the stomach with paralytic ileus in another, and in the fourth, following sudden death on the operating table, the interesting autopsy finding was *status lymphaticus*. The remaining case died of a tuberculous peritonitis.

The pneumoperitoneum therapy did not appear to bear any relation, either directly or indirectly, to the cause of death in any of these cases, with the possible exception of the last case.

This patient was first hospitalized in 1928 for bilateral pulmonary tuberculosis; pneumothorax was found impossible because of bilaterally adherent pleura, and, although the sputum became negative, the X-ray appearance and physical condition showed little change after two and one-half years of sanatorium treatment. He continued on a strict rest regimen at home, but he developed cavitation below the right clavicle with positive sputum in 1935. Pneumoperitoneum therapy was initiated immediately. Remarkable improvement resulted in the pulmonary lesions, and he was able to lead a modified normal life at home for one and one-half years, for the first time since the beginning of his illness. At the time of his death both the X-ray and autopsy findings showed a quiescent pulmonary tuberculosis without evidence of cavitation; gastric lavage had been negative for tubercle bacilli on two occasions on smear and guinea-pig inoculation. The peritonitis developed suddenly and death occurred two months later, in December, 1937, after thirty-one months of pneumoperitoneum therapy. The autopsy showed no mucosal lesions in the intestines and the histopathology of the peritoneum was characteristically that of a tuberculous peritonitis.

As tuberculous empyema at times occurs during the course of pneumothorax therapy without any obvious reason, it seems possible that tuberculous peritonitis might follow pneumoperitoneum therapy in the same way, the air and pressure acting as a local irritant. The above case, however, is the only one which we have seen that even suggests that this may have happened.

In analyzing this group, factors other than the air which might affect the autopsy findings were weighed as carefully as possible. We con-

sidered both the history of previous abdominal disease, such as surgical operations, pelvic inflammatory disease or tuberculous conditions, and the presence of abdominal tuberculous complications at autopsy.

The latter were of more importance in this regard, as would be expected in a group of patients with far advanced pulmonary tuberculosis. In most cases in which specimens were taken for microscopical study, the parietal peritoneum, at some distance from the site of needle puncture, was used. Thus any errors arising from such complications were reduced as much as possible. Nine patients (45 per cent) showed definite gastrointestinal tuberculosis, tuberculous mesenteric nodes, or both, and 3 (15 per cent) had tuberculous peritonitis. In this small group it is interesting to note how closely these figures approach the normal expectancy. Ophüls (8) in his *Statistical Survey of Three Thousand Autopsies*, performed at the Lane and San Francisco City and County Hospitals, found that secondary tuberculous infection of the gastrointestinal tract occurred in 46 per cent of the cases of active pulmonary tuberculosis and that tuberculosis of the peritoneum was present in 12.6 per cent of the cases of active tuberculosis.

The length of time during which pneumoperitoneum was continued varied from one to thirty-three months, as follows:

Months	1–3	4–6	7–12	13–24	25–33
Patients	6	5	3	4	2

In all cases enough air was given to obtain a good rise of the diaphragm as shown by frequent routine fluoroscopic and roentgenographic examinations. Other collapse therapy (pneumothorax, phrenic nerve operation, wax apicolysis, thoracoplasty) was used or attempted in combination with pneumoperitoneum in 28 instances.

Study of the autopsy findings revealed no consistent changes in any of the abdominal viscera which could be considered as due specifically to the pneumoperitoneum. The findings in regard to the peritoneum are shown in the following table:

Peritoneum at autopsy

PERITONEUM	NORMAL	TUBERCULOUS PERITONITIS	CHRONIC INFLAMMATION	
			Mild	Severe
Number of cases	11	3	3	3*

* One case judged secondary to underlying tuberculous complications.

In 15 (75 per cent) of the 20 cases, the peritoneum was considered to show no effects due specifically to the air and pressure. Of these, in 11 the peritoneum was normal. In one the underlying tuberculous complications were so extensive that they were regarded as responsible for the inflammatory changes present in the peritoneum.

This patient had a rapidly progressive, far advanced pulmonary tuberculosis and died three months after entry into the hospital. The intestines showed an extensive, ulcerative tuberculosis, the mesenteric nodes were involved, and the mesentery was red, thickened, rolled up on itself and bound down to the intestines with soft adhesions to the parietal peritoneum. The microscopical study of a section of the peritoneum showed a chronic inflammation. Prominent in the section are many areas of surface cell desquamation with replacement fibrosis. The fibrous tissue immediately beneath the mesothelial layer is loosely woven and there is scattered infiltration with inflammatory cells which in this instance are almost exclusively lymphocytes.

In 3 cases a tuberculous peritonitis was found and as this is about the normal expectancy according to Ophüls (8) the pneumoperitoneum does not appear to have been a causative factor.

In 5 cases (25 per cent) the autopsy and microscopical findings showed a chronic inflammation of the peritoneum which could be considered a result of air and pressure. In 3 of these 5 cases the degree of change was so slight that it appeared of little clinical significance as far as any ill effects on the well-being of the patient was concerned. In 2 of these, the peritoneum appeared grossly normal and the chronic inflammatory reaction was demonstrated only microscopically. The microscopical findings are as follows:

1: The peritoneum shows a chronic inflammatory reaction which appears entirely nonspecific. The blood supply is very free and the individual vessels are large and engorged. The mesothelial surface layer is made out with difficulty and the underlying tissues show some young fibroblasts with scattered bands of collagenous fibres. Infiltration with lymphocytes, plasma cells and macrophages is present, but the cell groups are small and scattered.
2: Sections from the peritoneum show slight, but nevertheless definite, evidences of a nonspecific inflammation. There is some desquamation of surface cells with small accumulations of lymphocytes in a slightly oedematous subserous tissue. The lymph channels are widened and there is perhaps a slight increase in the blood supply.

In the other case, which died of acute dilatation of the stomach with

paralytic ileus following a wax apicolysis, a mild thickening was apparent grossly.

The 2 remaining cases (10 per cent) showed a well marked chronic inflammation of the peritoneum. One of these had had an appendectomy four years previously and a salpingo-oophoritis was found at autopsy, but these complications appeared to play only a minor part in causing the peritonitis. The microscopical study of the peritoneum showed a chronic inflammation. Scarring was the most noticeable feature in this section, the peritoneum and its underlying structures being entirely replaced by broad hyalinized fibrous bands in parallel placement. Between the bands were a few scattered lymphocytes. The picture was that of an inflammatory process which had scarred, leaving very little evidence of active inflammation.

The other patient had an intense chronic inflammation which was complicated by 100 cc. of dark brown colored fluid of unknown aetiology. The microscopical study of the peritoneum showed a chronic inflammation. The inflammatory reaction seen in this case was more intense than that present in any of the other cases in this series. The histological picture was that of a relatively old process with an active and progressive type of chronic inflammation still in progress. The surface cells were in places desquamated, but where present showed a definite cuboidal type. Nowhere were the flat cells of a normal peritoneum found. There was some oedema in the subserous tissue and infiltration with lymphocytes, plasma cells and macrophages was pronounced. Fibrosis with hyalinization of fibrous bands was a prominent feature.

In neither case was the peritonitis the cause of death. The first died on the seventh day following an operation for wax plombage, and the immediate cause of death was pressure of the wax on the superior vena cava, with auricular fibrillation and cardiac decompensation. The other patient died with a terminal massive haemoptysis from an extensive pulmonary tuberculosis with multiple large cavities.

What would be the later clinical effects of such a chronic inflammation of the peritoneum as these last two cases showed, cannot be determined definitely at this time. Clinical observations on large series of cases over a long period of time will be necessary before any such after effects can be correctly appraised. We can say, however, that to date clinical observations have shown little cause for alarm, and that the present study of 20 cases of autopsy material reveals that inflammatory changes of any moment were limited to 2 cases.

The following table shows the relation between the condition of the peritoneum and the length of time during which the pneumoperitoneum therapy was administered:

Duration of therapy and appearance of peritoneum at autopsy

PERITONEUM	MONTHS OF PNEUMOPERITONEUM THERAPY				
	1-3	4-6	7-12	13-24	25-33
Normal	5	3	2	1	
Chronic inflammation:					
Mild		1		1	1
Severe	1*		1	1	
Tuberculous peritonitis		1		1	1

* Secondary to underlying tuberculous complication.

It will be seen that 10 of the 11 cases with normal peritoneum were among the 14 cases autopsied after treatment for a year or less. On the other hand, the cases showing a chronic inflammatory reaction of the peritoneum were divided equally between the one to twelve months group and the twelve to thirty-three months group. Obviously with only 6 cases of chronic inflammation, and only 6 cases in all who were treated for longer than a year, no conclusions can be drawn. It may be pointed out, however, for what it is worth, that a comparison of those receiving therapy for less than a year with those treated for a longer period of time reveals a distinctly higher percentage of chronic inflammation in the latter group. Nevertheless, the 2 cases of severe inflammation were found at autopsy after only eight and thirteen months of treatment, respectively, while 2 cases after twenty and thirty-three months showed chronic inflammation microscopically only. To summarize: as one would expect from what we know of the effect of air on the pleura in pneumothorax therapy, there seems to be a tendency for gradual thickening of the peritoneum with increasing duration of the pneumoperitoneum. However, the inflammatory changes may still be minimal after thirty-three months.

Ascites was present in varying amounts in 9 cases (45 per cent) as a terminal complication. Although the number of cases is small, two interesting observations can be made: (*1*) In this series it had been necessary to aspirate fluid only in the 3 patients with definite tuberculous peritonitis. From this we might conclude that, when large amounts of fluid appear as a complication during pneumoperitoneum therapy for pulmonary tuberculosis, tuberculous peritonitis should be suspected.

(*2*) Ascites, other than the very large amounts accompanying tuberculous peritonitis, even if present in quantities large enough to be diagnosed clinically, is not necessarily indicative of a chronic inflammatory reaction in the peritoneum. Excepting the cases of tuberculous peritonitis, there were 6 cases with ascites, divided equally between cases with normal peritoneum and those showing a chronic inflammatory reaction. The fluid was clear and straw-colored in all cases, except one which had 100 cc. of dark brown colored fluid complicating a chronic peritonitis. The amounts varied from 100 cc. to 2,000 cc. Of our cases with a chronic inflammation of the peritoneum, 3 were without fluid, 2 showed only small amounts and in only one case, in which the chronic inflammation was secondary to tuberculous complications, was a larger amount found. On the other hand, ascites was present in 3 cases with normal peritoneum and in moderately large quantities such as are occasionally seen clinically by fluoroscopy in 2 of these.

SUMMARY

Since pneumoperitoneum is recognized as one of the various collapse procedures available in the treatment of pulmonary tuberculosis, many patients are receiving air intraperitoneally. The therapeutic effects on pulmonary tuberculosis have been established. Clinical observations have shown few complications, and pneumoperitoneum therapy can be compared favorably with pneumothorax therapy in this regard. However, little is known of the local effects of the air on the peritoneum.

To determine more specifically the effect of long continued air and increased pressure on the peritoneum and abdominal viscera, an analysis was made of the autopsy and microscopical findings on 20 patients with pulmonary tuberculosis treated by pneumoperitoneum for from one to thirty-three months.

The pneumoperitoneum therapy apparently caused no consistent changes in any of the abdominal viscera. In 15 cases (75 per cent) the peritoneum showed no specific local effects. This autopsy material showed only 2 cases (10 per cent) with inflammatory changes of any moment which were apparently due to pneumoperitoneum. With increasing duration of therapy, a tendency for gradual thickening of the peritoneum was noticed, but the inflammatory change may still be minimal after thirty-three months of treatment.

Ascites was a terminal complication in 9 cases (45 per cent), but aspiration was necessary only in patients with tuberculous peritonitis.

The presence of ascites was not necessarily indicative of a chronic inflammatory reaction in the peritoneum, as in some instances the peritoneum was normal in the presence of moderately large amounts of fluid.

REFERENCES

(1) Overholt, R. H.: Air in the peritoneal cavity, Arch. Surg., 1930, *21*, 1283.

(2) Vajda, L.: Can one employ pneumoperitoneum in collapse therapy of bilateral pulmonary tuberculosis, Ztschr. f. Tuberk., 1933, *67*, 371. (Abstracted in J. A. M. A., 1933, *101*, 179.)

(3) Banyai, A. L.: Therapeutic pneumoperitoneum, Review of one hundred cases, Am. Rev. Tuberc., 1934, *29*, 603.

(4) Trimble, H. G., and Wardrip, B. H.: Pneumoperitoneum in treatment of pulmonary tuberculosis, Ibid., 1937, *36*, 111.

(5) Myers, J. A.: Encyclopaedia Britannica, 1938 Year Book, p. 665.

(6) Kountz, W. B., and Alexander, H. L.: Emphysema, Medicine, 1934, *13*, 251.
Symptomatic relief of advanced emphysema, Proc. A. Am. Phys., Washington, D. C., May, 1933, and Am. J. M. Sc., 1934, *189*, 660.

(7) Gordon, B.: The mechanism and use of abdominal supports in the treatment of pulmonary diseases, Am. J. M. Sc., 1934, *187*, 692.
Abdominal conditions influencing the lung and pleural pressure in pulmonary tuberculosis, Am. Rev. Tuberc., 1934, *30*, 72.
Results of abdominal compression in pulmonary tuberculosis, Ibid., 1935, *32*, 686.

(8) Ophüls, W.: A statistical survey of three thousand autopsies, Stanford University Press, Stanford University, California, 1926, pp. 131–180.

ACCIDENTAL PNEUMOPERITONEUM[1]

A Report of 8 Cases

L. R. GAETÁN

During the last three years we have been on the lookout for cases of accidental pneumoperitoneum some of which may be overlooked due to lack of symptoms or because no X-ray is taken soon enough after the initial attempt to establish an artificial pneumothorax. To avoid missing any case we have insisted on a routine fluoroscopic examination after every insufflation at the beginning of artificial pneumothorax treatment.

Our cases were collected in a 800 bed institution where there are as a rule 300 cases with artificial pneumothorax. We average about 31,000 insufflations a year. Our 8 cases of accidental pneumoperitoneum occurred over a period of three years, thus giving an average of one accidental pneumoperitoneum in 11,000 insufflations.

In all our cases this accident happened after repeated attempts to establish artificial pneumothorax. As different places in the chest must be tried the operator may strike one interspace too low and enter the peritoneal cavity. Theoretically on entering the peritoneal cavity the manometric pressures should be the reverse of those obtained in the chest, with inspiration and expiration. In none of our cases was the operator aware of any change in the oscillations of the manometer.

In 4 of our cases there were symptoms which made us suspect the presence of a pneumoperitoneum and in 2 of these instances the diagnosis was made before the patient was X-rayed. We feel that an initial artificial pneumothorax if done correctly and if a small amount of air is given (200 to 250 cc.) should not cause the patient to experience any discomfort. If there is any discomfort we immediately are on the lookout for accidental pneumothorax or pneumoperitoneum. The symptoms most frequently encountered are pain in the epigastrium with radiation to the shoulder blades or neck. On examination tympany may be found over the abdomen and subcutaneous emphysema may be present.

[1] From the Insular Antituberculosis Sanatorium, Río Piedras, Puerto Rico.

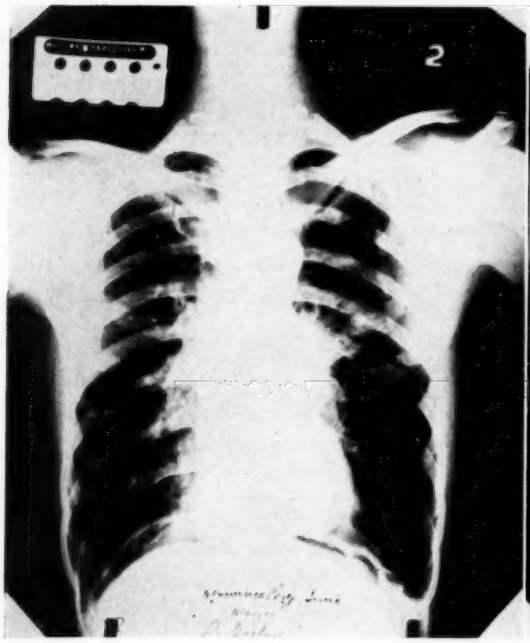


FIG. 1

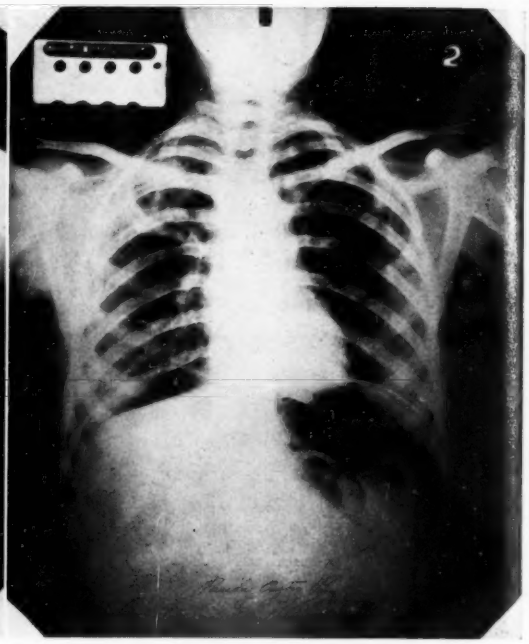


FIG. 2

FIG. 1. Case 3. Left pneumothorax, bilateral pneumoperitoneum
FIG. 2. Case 7. Bilateral pneumoperitoneum

TABLE 1

CASE NUMBER	AGE	SEX	COLOR	MANOMETRIC READINGS		AMOUNT OF AIR GIVEN	SYMPTOMS	SUBCUTANEOUS EMPHYSEMA	TYMPANY
				Start	End				
						cc.			
1	42	M	W	−7−5	−4−2	150	None		
2	53	M	W	−18−10	−8−4	300	Pain over epigastrium radiating to right shoulder	Yes	Yes
3	38	M	W	−10−6	−6−1	400	Pain over xiphoid	No	No
4	15	F	W	−6−4	−4−2	300	Pain in the neck	No	No
5	58	M	W	−10−7	−5−1	300	Pain in epigastrium radiating to left scapula	No	No
6	23	M	W	−6−2	−1,0	200	None	No	No
7	23	F	W	−10−4	−4,0	400	None	No	No
8	19	F	W	−6−3	−4−3	300	None	No	No

The symptoms disappear spontaneously but may last for a week. The accident was of no serious event in any of the cases.

Of special interest is one patient (case 3, figure 1) in whom a pneumoperitoneum was suspected because of pain over the xiphoid after a refill of an old established pneumothorax. The patient had had pneumothorax for one year, was arrested and working as clerk in the institution. A refill of 400 cc. of air was given with the needle inserted in the fourth interspace in the midaxillary line, the accustomed place of insertion in this individual case. The patient walked back to his work and after walking about 200 yards experienced a sharp pain over the xiphoid with no other symptom. He was able to walk back and was fluoroscoped immediately. A pneumoperitoneum was evident and confirmed by X-ray. There were no signs of spontaneous pneumothorax. The patient was reassured about the innocuousness of the accident and returned to work. The accident has not recurred in this patient.

SUMMARY AND CONCLUSIONS

1. Eight cases of accidental pneumoperitoneum during artificial pneumothorax therapy are reported.
2. Symptoms of pain in the epigastrium radiating to one of the shoulder blades occur quite frequently in cases of pneumoperitoneum.
3. Accidental pneumoperitoneum is not dangerous.
4. It is a rare accident that occurred about once in 11,000 insufflations.

CULTURAL METHODS IN THE DIAGNOSIS OF TUBERCULOSIS[1,2]

A Comparison of Four Types of Media with Animal Inoculation in the Detection and Isolation of the Tubercle Bacillus in Clinical Practice

HUGH G. WHITEHEAD

With the technical assistance of Miss Harriet Hicok

There are many methods for making a diagnosis of tuberculosis but none as reliable as the demonstration of tubercle bacilli. Failure to detect the causative organism is useful in excluding tuberculosis, if search for it is thorough and repeated. Too often search consists of casual examination of materials on direct smear, without recourse to concentration methods, culture or animal inoculation. The lack of acquaintance of physicians in general with modern methods of searching for the tubercle bacillus may explain the frequent failure to confirm a diagnosis of tuberculosis by detecting the organism. Many persons are admitted to sanatoria with a diagnosis of pulmonary tuberculosis having never had a sputum examination. The greater part are soon found to have active tuberculosis. Some are encountered, however, with nontuberculous pulmonary disease. Thorough sputum studies, failing to demonstrate the tubercle bacillus, would give a valuable clue to their true character. Pinner (24) in 1928 pointed out the value of a negative sputum after search by a combination of smear, culture and animal inoculation. Of 585 persons supposed to have tuberculosis, 83 had repeatedly negative sputum examinations. Of the 83, 33 were soon proved to be definitely nontuberculous and 14 had no pulmonary lesion. Of the remaining 36 with roentgenological evidence of pulmonary tuberculosis, only 5 were found, on prolonged clinical and roentgenological observation, to be active. At the same time he pointed out that the tubercle bacillus is found in 99 per cent of clinically active pulmonary cases, provided a thorough search is carried out. The great value of repeated search for the Koch bacillus is widely acknowledged, yet the improved

[1] From the Department of Medicine, Johns Hopkins Hospital, Baltimore, Maryland.

[2] Presented at a meeting of the Johns Hopkins Medical Society, Baltimore, Maryland, May 9, 1938.

methods for its detection available to-day are not generally appreciated. Krause (13) and Corper (3) in 1928 and more recently Greenberg and Cohn (9) have forcibly called attention to the inadequacy of routine search for tubercle bacilli as generally carried out, and the poor technique often observed even in first-class hospitals and clinics.

Opinion as to what constitutes a "proper search" for the Koch bacillus has changed constantly. For many years smears and animal inoculations were considered adequate, and culture of the organism was only of academic interest. In the light of our knowledge of acid-fast saprophytes, it soon became evident that simply finding the acid-fast organisms in smears by no means clinched the diagnosis. The animal method is far from ideal, being both expensive and troublesome. Only in recent years have cultural methods in diagnosis come to be appreciated.

The efficiency of the cultural method in the demonstration of the tubercle bacillus depends in no small part on the method of concentration. Concentration of materials to be examined was suggested as long ago as 1886 by Biedert (1) whose method was soon modified by Muhlhauser (19), Czaplewsky and Hensel (5), Uhlenhuth and Xylander (28), and in more recent years by Petroff (23), Sumiyoshi (27), Evanoff and Sweany (8), Corper (4), Hohn (10), and Loewenstein (16). In brief, the ideal concentrating material must have a maximum bactericidal or bacteriostatic effect on contaminants, a decided lytic effect on mucus, pus and protein debris and a minimum devitalizing effect on tubercle bacilli.

Of greatest importance, of course, is the type of media used. In his first studies Koch (12) used blood serum. The use of potato was suggested by Pawlowsky (21) and glycerol by Nocard and Roux (20). Dorset (6), Capaldi (2), and Lubenau (18) introduced the use of egg. The difficulty experienced in isolating the tubercle bacilli and of cultivating them after isolation delayed the use of the cultural methods in the diagnosis of tuberculosis. More efficient media have been developed in the past decade, the literature becoming voluminous with various types and modifications. Each type as introduced usually receives its greatest approbation from its originator. Several reports claim the cultural method to equal in reliability the animal inoculation method. A few claim the cultural method to be superior to the inoculation of a guinea pig. Practically all types use some combination of the fundamental ingredients: protein, carbohydrate, fat and minerals, in the form of egg, milk, cream, potato, glycerol and serum or amino acids, such as asparagin. More recently various mineral salts have been advocated as buffer agents

in maintaining a constant hydrogen-ion concentration, and some type of dye such as gentian violet, malachite green or congo red is sometimes added in minute amounts as a bacteriostatic agent against common contaminants. The effect of adding certain vitamins has been studied, with equivocal results. All media so far recommended for the isolation of tubercle bacilli are solid, with the exception of Corper's substrate (1932). Pinner (24) wrote in 1932, "The choice of a concentration method and of a suitable medium is still much discussed. Each method and each medium has its advocates, the most emphatic advocate being usually the originator of the particular procedure. A careful survey of the literature leaves one undecided as to the respective merits of each procedure." A recent survey still leaves one undecided. One fact stands out in the maze of reports on the subject. There are few reports of suitable comparative tests of media types, under clinical laboratory conditions, and properly controlled with animal inoculations. Eisendrath (7) has recently called attention to the inadequacy of such work in an excellent summary of the problem. In Schwabacher's (25) recent work only suspensions were used.

At the Johns Hopkins Hospital and Dispensary specimens of various materials suspected of being tuberculous are received at a central laboratory. Some are grossly contaminated with yeasts, spores, molds and fungi which resist acids and alkalis and which, on inoculation on media, cause gross contamination and make the media entirely unsuitable for isolation of tubercle bacilli. Some specimens are scant and dried by the time they reach the laboratory. This undoubtedly is the experience in any large general hospital or dispensary where the proper collection of materials is not fully appreciated by either the physicians or the patients. It is now recognized that the choice of laboratory procedures must be varied according to the character of the specimen. In the evaluation of a medium, consideration must also be made of expense, speed of diagnosis, facility and its efficiency in isolating tubercle bacilli, not only from sputum, but from many other types of materials. Its resistance to contamination is also a most important characteristic to ascertain.

EXPERIMENTAL

In view of the controversy encountered in the literature on the subject it was decided to carry out comparative tests on four types of media and control these tests with animal inoculations. The types of media chosen for the tests are so representative as to be called "standard." They were

Petroff's gentian-violet-egg (23), Loewenstein's modification of egg medium (17), Corper's glycerol-potato (3), and Petragnani's medium (22). Congo red dye was used in Loewenstein's medium, crystal violet with Corper's and malachite green with Petragnani's. Preliminary trial, personal correspondence with, and reports by other workers decided us to discard the medium recommended by Dorset (6), and those advocated by Sweany and Evanoff (8), Long (15) and Lubenau (18), as being comparatively inefficient or having other undesirable characteristics.

Collection of sputum specimens: For collection of a sputum specimen over a period of several days or a week a large container with tight-fitting top is used, similar to those used in collection of stool specimens (see figure 1). For collection at bedside from ward patients the usual loose-lid type of container is used. For clinic patients with ample expectoration the small "Estes" container is used.

Examination of specimens: Direct smears, concentration with 5 per cent oxalic acid (if specimen is not sterile), smears of the concentrated sediment, inoculation on two tubes of each type of medium and guinea-pig inoculation were carried out uniformly on each specimen submitted to the test. Materials were taken at random, regardless of their character, the clinical picture presented by the patient or the results of previous laboratory examinations.

Technique: The direct smears were made from a suitable portion, according to the type of material examined. In the case of sputum a cheesy or blood-tinged fleck was selected, as usual. Urine and other body fluids such as pleural, ascitic or cerebrospinal fluid were centrifuged and a smear made from the sediment. In the case of pus, a loopful was smeared out without other treatment. In searching for acid-fast organisms in venous blood and faeces direct smears were not made.

The concentration of materials was done by diluting with equal parts of 5 per cent oxalic acid, mixing thoroughly, and incubating at 37.5°C. for thirty minutes. The mixtures were centrifuged, after incubation, at 1500 r.p.m. for thirty minutes. Two types of centrifuge tubes were used (see figure 1). A 25 cc. tube was used for small amounts of material, and a 250 cc. capacity tube for larger collections, such as a twelve-hour collection of sputum from a case of bronchiectasis with copious sputum. After centrifuging, the supernatant fluid was poured off, the sediment neutralized with 4 per cent sodium hydroxide, and smears were made from the sediment. The tubes were then inoculated in the usual manner, and cotton plugs were placed loosely in the tubes. A special filing card (see

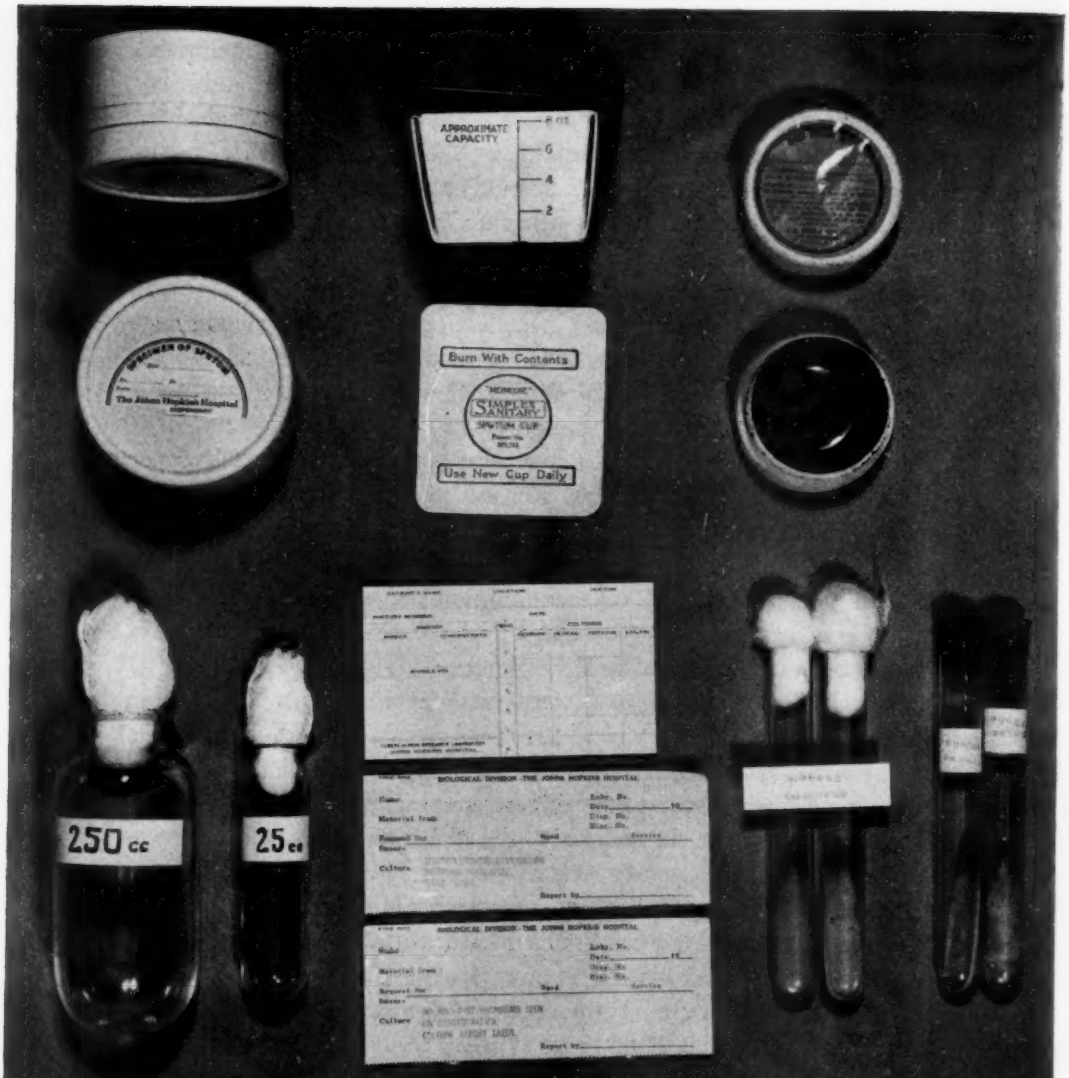


FIG. 1. Types of containers used in the collection of sputum specimens. Upper left—tight-fitting top paraffin cup for collection over period of several days. Upper centre—loose-top cup for use of ward patients. Upper right—"Estes" cup for use of clinic patients with copious expectoration. Lower left—types of centrifuge tubes used in concentration of materials. Lower centre—forms for keeping records of specimens. Lower right—tubes and labels.

FIG. 3. Special boxes arranged in incubator. Any specimen may be quickly and easily reached at any time by referring to the filing cards on each box.

FIG. 2

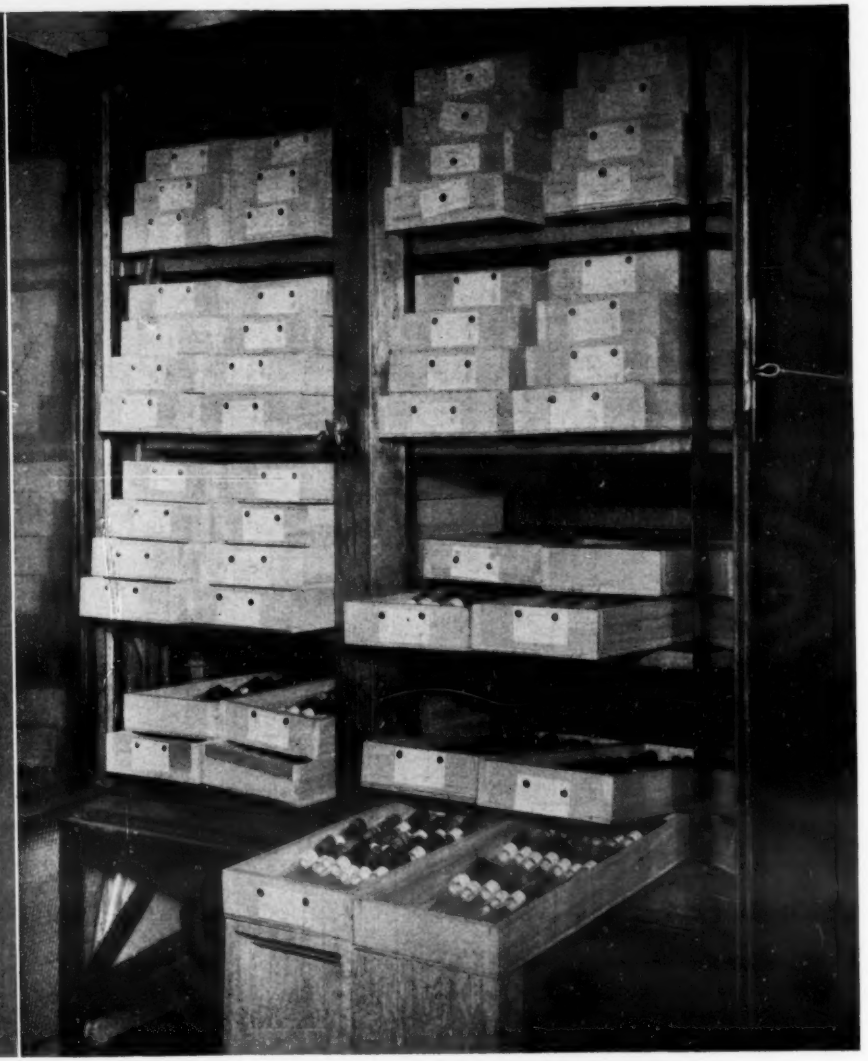


FIG. 3

FIG. 2. Special types of boxes for incubation of culture tubes, and rubber stoppers used to prevent drying of media.

FIG. 3. Special boxes arranged in incubator. Any specimen may be quickly and easily reached at any time by referring to the filing cards on each box.

figure 1) was used to record the result of the smears, and weekly observations of the tubes, and the guinea pig. The tubes were slanted in special boxes (see figures 2 and 3) and placed in the incubator at 37.5°C. After forty-eight hours the cotton plugs were replaced by sterile rubber stop-

TABLE 1

A comparison of culture and guinea pig inoculation of 215 miscellaneous specimens

NUMBER OF SPECIMENS	POSITIVE ON DIRECT SMEAR	POSITIVE AFTER CONCENTRATION	POSITIVE ON CULTURE	POSITIVE ON ANIMAL INOCULATION	POSITIVE BY ANY ONE METHOD	CULTURE POSITIVE, GUINEA PIG NEGATIVE*	GUINEA PIG POSITIVE, CULTURE NEGATIVE
215	12	10	31	32	41	7	5

* Four guinea pigs died prematurely (before six weeks).

TABLE 2

A comparison of four standard types of media for the isolation of the tubercle bacillus

NUMBER OF SPECIMENS CULTURED	POSITIVE ON PETRAGNANI'S MEDIUM	POSITIVE ON LOEWENSTEIN'S MEDIUM	POSITIVE ON CORPER'S POTATO MEDIUM	POSITIVE ON PETROFF'S MEDIUM
215	29	11	8	4

TABLE 3

A comparison of four standard types of media for the isolation of the tubercle bacillus in regard to contaminations

NUMBER OF TUBES OF EACH MEDIUM INOCULATED	NUMBER OF TUBES OF PETRAGNANI'S MEDIUM CONTAMINATED	NUMBER OF TUBES OF CORPER'S POTATO MEDIUM CONTAMINATED	NUMBER OF TUBES OF LOEWENSTEIN'S MEDIUM CONTAMINATED	NUMBER OF TUBES OF PETROFF'S MEDIUM CONTAMINATED
386	47 (12%)	52 (13%)	98 (25%)	98 (25%)

TABLE 4

A comparison of the relative efficiency of direct smear, concentration and culture on four standard media in the detection of the tubercle bacillus in miscellaneous types of materials

(These specimens were not examined by animal inoculation)

NUMBER OF SPECIMENS EXAMINED	POSITIVE ON DIRECT SMEAR	POSITIVE ON CONCENTRATION	POSITIVE ON PETRAGNANI'S MEDIUM	POSITIVE ON LOEWENSTEIN'S MEDIUM	POSITIVE ON CORPER'S POTATO MEDIUM	POSITIVE ON PETROFF'S MEDIUM
190	21	19	29	9	8	8

pers, to prevent escape of moisture and drying of the media. Upon the appearance of a suspicious looking growth, even when obviously a contaminant, smears were immediately made and the exact nature of the growth ascertained. The cultures were observed weekly for six

weeks for evidence of macroscopical growth of tubercle bacilli, and monthly thereafter for three months. If negative after three months they were discarded. All colonies considered to be tubercle bacilli were smeared and their acid-fast nature verified by staining. If there was reason to doubt the pathogenicity of the organisms thus isolated, because of their morphology, type of colony, rate of growth or chromogenicity, their pathogenicity for guinea pigs was immediately tested.

All animals inoculated were carefully observed weekly for adenitis. If a lymph node appeared at the site of injection the guinea pigs were killed in six weeks; otherwise in ten weeks. If no evidence of tuberculosis was found at autopsy, sections of the tissues were made and studied for the presence of acid-fast organisms or specific tissue changes.

RESULTS

The results are summarized in tables 1, 2, 3 and 4.

DISCUSSION

Under the conditions of the experiment, Petragnani's medium was found to be by far the most efficient and the most satisfactory from the point of view of contamination, compared to the types advocated by Loewenstein, Corper and Petroff. It has the additional desirable features of being easy to prepare and inexpensive. It will not, however, withstand the sterilization necessary to dehydration for commercial preparation. Since there were a significant number of specimens positive on one of the three other types tested when negative on Petragnani's medium, it would seem desirable to use routinely all four types, plus animal inoculation on specimens proving negative on direct and concentrated smear examination.

The factor of speed in diagnosis in the cultural methods was not closely studied. Reports in the literature of this phase of the cultural methods are vague and indefinite. When "positive" is reported it is not generally clear whether macroscopical or microscopical culture is implied. Reports are made of scraping the surfaces of cultures at regular intervals and searching for acid-fast organisms. In this way a positive finding may occasionally be reported much earlier than awaiting the formation of a macroscopical colony. This method was not used in our study, for several reasons. First, we endeavored to simulate the working conditions of a general laboratory, and such procedure does not seem practical where large numbers of routine specimens are to be examined. Secondly, it is felt that scraping the surface of a culture with a loop at regular

intervals would tend to disturb the growth, which at best is difficult to obtain, and might result in the failure of development of macroscopical colony growth. Kahn (11) has shown that the small non-acid-fast granules may be the youngest forms, and the progenitors of the acid-fast tubercle bacillus. These are the forms likely to be disturbed by scraping, yet would not permit of a diagnosis of tuberculosis. The situation is comparable to that encountered in the inoculation of animals. We usually allow six weeks before sacrifice, although there may be a well-defined regional adenitis and a dissemination at a much earlier date. Suffice it to say that some positive cultures were obtained macroscopically as early as five days after inoculation, and others as late as three months. The average time required for the appearance of a colony was four weeks.

Contaminations were unusually frequent in this series, compared to reports from studies in various sanatoria. As pointed out above, our specimens were taken at random from dispensaries, general medical and surgical wards, often over five-day periods. Gross contamination under such circumstances is the rule rather than the exception. Investigation reveals that rarely are the patients instructed by their physicians in the proper method for collecting the specimen to be examined. Contaminating molds, yeasts, fungi and saprophytic acid-fast organisms, while probably not as resistant to acids, alkalis and dyes as are tubercle bacilli, nevertheless may easily survive exposure to concentrating materials as strong as may be used without seriously devitalizing the tubercle bacilli. Throughout the experiment careful attention was paid to glassware, the manufacture of the media, sterilization tests before using the media and general technique, and the high percentage of contaminations cannot be attributed in significant measure to these factors.

CONCLUSIONS

1. A total of 215 specimens of various types were examined for tubercle bacilli by direct and concentrated smears, culture on two tubes each of four types of media and animal inoculation. Concentration did not increase the number of positives, but satisfactorily prepared the material for culture and injection into a guinea pig. Culture and animal inoculation increased the number found on smear.

2. Petragnani's medium showed more efficiency in promoting growth of tubercle bacilli and more resistance to contamination than did the media

recommended by Loewenstein, Corper, or Petroff for isolation from contaminated materials.

3. A series of 190 specimens without animal controls showed a similar superiority of Petragnani's medium.

4. Greater efficiency of the culture method is obtained by using several different types of media in routine laboratory search for the tubercle bacillus. Available data do not warrant the substitution of the culture method for the animal method, but indicate that both should be used for the maximum reliability in laboratory diagnosis of tuberculosis.

REFERENCES

(1) Biedert: Ein Verfahren, den Nachweis vereinzelter Tuberkelbazillen zu sichern, nebst Bemerkungen über die Färbbarkeit der Bazillen und Aetiologie der Tuberkulose, Berl. klin. Wchnschr., 1886, *23*, 713.

(2) Capaldi, A.: Zur Verwendung des Eidotters als Nährbodenzusatz, Centralbl. f. Bakt., 1896, *20*, 800.

(3) Corper, H. J., and Uyei, N.: The cultivation of tubercle bacilli. An improved method for isolation from tuberculous materials, J. Lab. & Clin. Med., 1928, *13*, 469.

(4) Corper, H. J., and Uyei, N.: The isolation of tubercle bacilli from contaminated tuberculous materials, Am. Rev. Tuberc., 1927, *16*, 299.

(5) Czaplewsky and Hensel: Zum Nachweis der Tuberkelbazillen im Sputum, Ztschr. f. Tuberk., 1900, *1*, 387.

(6) Dorset, M.: The use of eggs as a medium for the cultivation of bacillus tuberculosis, Am. Med., 1902, *3*, 55.

(7) Eisendrath, D. N.: International Abstract of Surgery, Surg., Gynec. & Obst., 1927, *65*, 2.

(8) Sweany, H. C., and Evanoff, M.: The isolation of tubercle bacilli from septic material, Am. Rev. Tuberc., 1928, *17*, 47.

(9) Greenberg, M., and Cohn, M.: The certified diagnosis of tuberculosis, Ibid., 1937, *36*, 126.

(10) Hohn, J.: Kultur der Tuberkelbazillen, Centralbl. f. Bakt., 1926, *98*, 460.

(11) Kahn, M.: Moving pictures of development of bacteria from single cell, Natl. Tuberc. A. Tr., 1935, p. 144.

(12) Koch, R.: Die Aetiologie der Tuberkulose, Berl. klin. Wchnschr., 1882, *29*, 221.

(13) Krause, A. K.: Remarks on the laboratory diagnosis of pulmonary tuberculosis, Am. Rev. Tuberc., 1928, *18*, 51.

(14) Lawson, G. B.: Am. J. Clin. Path., July, 1937, p. 30, Tech. Supplement.

(15) Long, E. R., and Campbell, L. K.: Am. Rev. Tuberc., 1922, *6*, 636.

(16) Loewenstein, E.: Beitrag zur Leistungsfähigkeit der direkten Züchtung der Tuberkelbazillen aus infectiösem Material, Wien. klin. Wchnschr., 1924, *37*, 231.

(17) Loewenstein, E.: Die Züchtung der Tuberkelbazillen aus dem strömenden Blute, Centralbl. f. Bakt., 1931, *120*, 127.

(18) Lubenau, C.: Der Eigelbnährboden als Ersatz des Serums zur Kultur von Diphtherie und Tuberkelbacillen, Hyg. Rundschau, 1907, *17*, 1455.

(19) Mulhauser: Über das Biedertsche Verfahren zum Nachweis von Tuberkelbazillen, Deutsche med. Wchnschr., 1891, *17*, 282.

(20) NOCARD AND ROUX: Sur la culture du bacille de la tuberculose, Ann. Inst. Pasteur, 1888, *1*, 19.

(21) PAWLOWSKY, A. D.: Culture des bacilles de la tuberculose sur la pomme de terre, Ibid., 1888, *2*, 303.

(22) PETRAGNANI, G.: Terreno e tecnica per l'isolamento in cultura pura dei B. di Koch dagli escreati a da altri materiali tubercolari, Atti d.r. Accad. d. fisiocrit. in Siena, 1926, *1*, 177.

(23) PETROFF, S. A.: A new and rapid method for the isolation and cultivation of tubercle bacilli directly from the sputum and feces, J. Exper. Med., 1915, *21*, 38.

(24) PINNER, M.: Sputum examination in pulmonary tuberculosis, J. Lab. & Clin. Med., 1932, *17*, 611.

(25) SCHWABACHER, H.: Comparison of different media for growth, Tubercle, 1937, *18*, 199.

(26) SWEANY, H. C., AND EVANOFF, M.: The isolation of tubercle bacilli from septic material, Am. Rev. Tuberc., 1928, *17*, 47.

(27) SUMIYOSHI, Y.: Beitrag zur Reinzüchtung von Tuberkelbazillen aus dem Sputum, Ztschr. f. Tuberk., 1924, *39*, 5.

(28) UHLENHUTH AND XYLANDER: Antiformin, ein bakterienauflösendes Desinfektionsmittel, Berl. klin. Wchnschr., 1908, *45*, 134.

EDITORIAL

Tuberculin Anergy and the Variability of Tuberculins

The question of anergy to tuberculin in the presence of presumptive tuberculosis has been the subject of much discussion in recent months. Especially noteworthy for the interest excited have been the carefully conducted and concisely reported studies of Lumsden, Dearing and Brown (1) on tuberculous infection in school children in Coffee County, Alabama and Giles County, Tennessee. These investigators compared the incidence of positive reaction to several different kinds of tuberculin, in relation to the incidence of lesions diagnosed as tuberculosis in X-ray films, and found not only a lack of correlation between the tuberculin reaction and the presence of shadows in the X-ray film interpreted as representative of tuberculous lesions, but a wide discrepancy in the percentage of positive reactions to different samples of tuberculin. The lack of correlation between tuberculin reaction and X-ray examination was most conspicuous in films showing shadows interpreted as calcified lesions of primary tuberculosis.

Numerous articles of similar import could be cited on the absence of tuberculin allergy in cases with presumptive evidence of old tuberculous infection in the form of calcified intrathoracic masses, but the reader need recall only the several reports appearing in the REVIEW within the last year, namely, those by Nelson, Mitchell and Brown (2) from Ohio, Gass, Gauld, Harrison, Stewart and Williams (3) from Tennessee and Crimm and Short (4) from Indiana. All of these observers have emphasized the frequency of negative reactions in the presence of pulmonary calcifications, a frequency ranging in the different series and in the hands of different observers from 17 to 46 per cent.

As noted, these various studies have provoked widespread comment. It is not the fact that allergy may be absent in the presence of calcified lesions that is surprising, but that this may occur so frequently. Failure of reaction in the presence of calcified nodules is an old observation familiar to all workers in the field. McPhedran and Opie (5), summarizing an extensive Philadelphia experience in 1935, stated that "calcified tuberculous foci were found in approximately 5 per cent of persons who

failed to react to tuberculin." In passing, it may be noted that in the first article published on the use of the Purified Protein Derivative of Tuberculin certain cases with pulmonary calcification were recorded, with failure of reaction either to this type of tuberculin or to Old Tuberculin.

The majority of investigators in the past have interpreted these cases as illustrations of obsolete infection, and there is increasing reason to accept this explanation for some, if not a large proportion. Specific examples with calcification, once positive and subsequently of lowered sensitivity or even negative to tuberculin, have been frequently recorded since the cases so thoroughly worked up by Krause (6), whose observations on the relation of the intensity of the tuberculin reaction to the extent and activity of tuberculous lesions have been widely quoted. A plausible explanation of the waning of allergy is to be found in the recently reported finding by Feldman and Baggenstoss (7) of sterility in most old calcareous foci of primary infection.

Still more direct and significant evidence, however, on the waning of allergy with recovery from active lesions of tuberculosis is available in the records of BCG vaccination. Hundreds of thousands of human beings have been deliberately inoculated with controlled dosage of the attenuated but living BCG, and numerous careful records have been kept of the intensity of the tuberculin reaction in relation to the course of infection set up. In the overwhelming majority of cases, indeed in practically all of those infected intracutaneously with 0.15 mg. BCG or more, the reaction becomes positive in a few weeks. After reaching a period of maximum intensity it then tends to wane. "In a considerable percentage of cases," according to Kereszturi, Rosenberg and Park (8), "the tuberculin allergy becomes less intensive between six and twelve months after vaccination and gradually becomes negative after twelve months."

In the light of these observations of complete healing with eventual sterility of spontaneous human lesions, on the one hand, and decrescence and disappearance of the allergy produced by artificial human infection, on the other, it would not be surprising if the tuberculin reaction eventually became negative in *all*, not merely many, cases of calcified primary lesions, provided no further infection occurred. Indeed there is good reason to believe that, in many cases of positive tuberculin reaction in the presence of calcified foci of tuberculous infection, the reaction is positive not because of the presence of the calcified lesion but because of a later

superinfection. Crimm and Short (4) have called attention to this possibility in recording the recurrence of allergy in a few cases with calcification, previously negative to tuberculin.

Altogether there is good reason to believe that allergy, conferred originally by an active tuberculous lesion of the childhood type, can disappear completely, to recur only with new superimposed infection. With the general decline of tuberculosis in the community, with corresponding lessening opportunity for reinfection, it is only to be expected that an increasing number of nonreacting cases with calcification will be found. It is well to keep the fact in mind that the calcified lesions discovered in any survey to-day represent not the index of tuberculous infection of the present period, but the remains of tuberculous infection in the past. This may not be a new, but it seems to be a frequently overlooked concept of tuberculous infection.

However, there is still room for doubt that all the lesions commonly diagnosed as calcified nodules of primary tuberculosis are really tuberculous. The nontuberculous nature of many, indeed, has been pointed out by Frimann-Dahl and Waaler (9). Particularly in a community where calcifications are present in half of the adolescent population, as in certain of the regions studied by Lumsden and Gass and their colleagues, it is pertinent to inquire if there could be any other cause than tuberculosis for the calcifications found. Studies so directed, as a matter of fact, are in prospect.

Anergy in the presence of active tuberculosis of the primary or "childhood" type has been less frequently recorded. It will be generally conceded that some cases merely represent delay in the appearance of allergy. A decade ago McPhedran (10) pointed out that X-ray evidence of developing primary tuberculous infiltration of the lung may precede the development of a positive reaction, and others have repeatedly confirmed the observation. Anergy in the presence of well established lesions believed to be tuberculous is subject to much uncertainty, because of the difficulty in proving the diagnosis of primary tuberculous infection in these cases. The shadow itself is not distinctive, and more frequently than not the diagnosis cannot be established on the basis of a single film. It is the course of the lesion rather than its character, as seen in the X-ray film, that is important. Infiltrations that disappear are apt to be of pyogenic origin; those that persist some months are considered as probably tuberculous. It is a fact that most of the reported cases of anergy in the presence of active primary tuberculosis

have not been given the benefit of this time trial. A diagnosis based on persistence of the infiltration, however, is still subject to much question, for increasing understanding is bringing to light other causes for such infiltrations, such as unresolved pyogenic infections, bronchiectasis, the all too frequent aspiration of oil, etc. In brief, in a case of tuberculin anergy in the presence of supposed active primary tuberculosis, the burden of proof is on the diagnosis of tuberculosis.

The question of tuberculin anergy in the presence of supposed tuberculosis is further complicated by the fact that allergy to tuberculin is usually absent in a group of diseases, including Boeck's sarcoid, *ostitis tuberculosa multiplex cystoides*, uveoparotid fever and certain cases of Mikulicz's syndrome, bearing great anatomical similarity to tuberculosis. Pinner (11) has comprehended these diseases, together with certain related lesions clinically and anatomically less well defined, under the general term "noncaseating tuberculosis." The tuberculin anergy of these cases has usually been considered evidence that they are not tuberculous, but the demonstration of blood-stream anticutins and the occasional transformation of the lesions into typical tuberculosis (see Horton, Lincoln and Pinner (12)) make exclusion from the category of tuberculosis unjustifiable on the basis of tuberculin anergy alone. The question cannot be settled until the reasons for allergy are better understood. There is evidence that tuberculin allergy is related to the phenomenon of caseation. It is entirely possible, as Pinner has suggested, that the pathological conditions listed are not types, but rather phases of tuberculosis, and that tuberculin anergy is characteristic of the noncaseating phase. Obviously much further study is needed.

As to the necessity of a reliable tuberculin there can be no argument. It is true and has been known for years that the various preparations of Old Tuberculin on the market vary greatly in their capacity to elicit reaction. Both their strength and their specificity of action have been subject to question. It was exactly this fact that led to the search for a substance of specificity, stability and constant potency, that could be substituted for the highly variable Old Tuberculins in use. It is hoped that the Purified Protein Derivative of Tuberculin will fulfil this need. The discovery by Lumsden, Dearing and Brown of a weak sample of the Purified Protein Derivative, not measuring in strength with another sample selected, is evidence that the present commercial production of this purified substance is subject to error. It is a cause of serious concern to those interested in the development of a standard tuberculin of uni-

form potency. There can be no disagreement with the statement of these authors that, "Further work, both laboratory and field, by properly equipped agencies, for the determination of reliable standards of potency, specificity, uniformity and stability of tuberculin preparations and for the establishment of reliable standard methods of administration of tuberculin tests among persons is highly in order." There is every reason to believe that such work is forthcoming.

From current comment, however, it would seem that the concern justly provoked by such studies as those cited in the foregoing paragraphs has been extended to certain types of public health endeavor for which there is no implication. For present purposes a clear distinction must be drawn between tuberculin-X-ray surveys for the separate purposes of determining the infection index regardless of morbidity, and tuberculosis case-finding. No serious doubt has been expressed over the value of tuberculin as a mechanism for detecting ordinary cases of pulmonary tuberculosis. The studies cited, which have been widely publicized in recent months, do not deal with this subject. On the other hand, studies of the tuberculin reaction covering more than thirty years, carried out on tens of thousands of tuberculous patients in sanatoria and dispensaries, show that the overwhelming majority of patients with frank tuberculosis are positive to tuberculin and, moreover, that they react to small doses and to most if not all of the many types of tuberculin on the market. It may be objected that the sanatorium and dispensary do not furnish a sufficiently severe test of the case-finding capacity of tuberculin. One need only turn, however, to what are generally conceded to be the best conducted case-finding programs in the country, those carried out in schools of medicine and nursing. Here a close correlation of positive tuberculin tests and active cases has been the rule. The cases found on first examination are in the tuberculin-positive group. Those discovered later are in the same group or in students who have subsequently become positive to tuberculin. In most of these continuous surveys the students are subjected to both tuberculin test and X-ray examination, and while clinical disease has not infrequently been observed to develop with alarming rapidity after the development of a positive tuberculin reaction, there is no proved record of its development in the absence of a positive reaction.

In the light of this abundant experience no reason is apparent to depart from the present established custom of using tuberculin in case-finding programs. Its relative value as a screen before X-ray examination, or

as an adjunct to X-ray examination, will depend on local conditions, particularly the proportion of the group that are positive, as always.

On the other hand, good reason has been given for pause in our efforts to determine epidemiological indices of the amount of infection until more knowledge is obtained. One fact that already seems clear is that we must establish a definition of "infection." The concept that is finally adopted will have to meet the issue of existing as opposed to obsolete invasion by tubercle bacilli. From a practical standpoint it seems doubtful whether there is nearly as much significance in determining how many persons have ever been infected by tubercle bacilli, as in finding how many have been recently infected or harbor bacilli at the moment. Whether this can be done or not remains to be seen in the light of future research.

REFERENCES

(1) Lumsden, L. L., Dearing, W. P., and Brown, R. A.: Questionable value of skin testing as a means of establishing an epidemiological index of tuberculous infection, Am. J. Pub. Health, 1939, *29*, 25.

(2) Nelson, W. E., Mitchell, A. C., and Brown, E. W.: The intracutaneous tuberculin reaction associated with calcified intrathoracic lesions, Am. Rev. Tuberc., 1938, *37*, 311.

(3) Gass, R. S., Gauld, R. L., Harrison, E. F., Stewart, H. C., and Williams, W. C.: Tuberculosis studies in Tennessee, Ibid., 1938, *38*, 441.

(4) Crimm, P. D., and Short, D. M.: Tuberculin anergy in cases with pulmonary calcifications, Ibid., 1939, *39*, 64.

(5) McPhedran, F. M., and Opie, E. L.: The spread of tuberculosis in families, Am. J. Hyg., 1935, *22*, 565.

(6) Krause, A. K.: Human resistance to tuberculosis at various ages of life, Am. Rev. Tuberc., 1925, *11*, 303.

(7) Feldman, W. H., and Baggenstoss, A. H.: The residual infectivity of the primary complex of tuberculosis, Am. J. Path., 1938, *14*, 473.

(8) Kereszturi, C., Rosenberg, H. A., and Park, W. H.: Tuberculin allergy produced by parenteral BCG vaccination, Am. Rev. Tuberc., 1937, *36*, 90.

(9) Frimann-Dahl, J., and Waaler, G.: Röntgenologische und pathologische-anatomische Studien über den tuberkulösen Primärkomplex, Acta Radiologica Supplementum xxxiii, 1936. Reviewed, Am. Rev. Tuberc., 1938, *37*, 117.

(10) McPhedran, F. M.: The diagnosis and classification of pulmonary tuberculosis in childhood and adolescence, Am. Rev. Tuberc., 1929, *20*, 532.

(11) Pinner, M.: Noncaseating tuberculosis, Ibid., 1938, *37*, 690.

(12) Horton, R., Lincoln, N. S., and Pinner, M.: Noncaseating tuberculosis, Case reports, Ibid., 1939, *39*, 186.

Esmond R. Long

HAEMATOGENOUS TUBERCULOSIS IN THE ADULT[1]

I. Generalized Haematogenous Tuberculosis

ELI H. RUBIN

PATHOGENESIS

Tubercle bacilli may invade the blood-stream at any stage of tuberculosis and at any age: following the primary infection, during the evolution of the disease and as a terminal event. The stage of the disease influences considerably the incidence of haematogenous implantations in the various organs of the body; the age of the patient plays a minor rôle. Every form of haematogenous tuberculosis in the infant and child is also seen in the adult. Chronic forms of haematogenous tuberculosis are uncommon in children because the latter, as a rule, do not live long enough to allow time for the protracted manifestations of the disease to develop.

When tubercle bacilli invade the blood-stream there may result a generalized miliary tuberculosis that overwhelms the patient within a few weeks or there may be complete absence of symptoms. Between these extremes there is a wide range for various manifestations of haematogenous tuberculosis in parts of organs, whole organs or groups of organs depending on the numbers and virulence of the tubercle bacilli, the frequency with which they invade the blood-stream, the site where they enter the blood-stream and the sensitivity of the body to tuberculotoxins.

In a recent, exhaustive study, Wilson (23) estimated that tubercle bacilli have been demonstrated in the blood in about 4.9 per cent of patients with severe pulmonary tuberculosis, in about 2.7 per cent of patients with nonpulmonary tuberculosis and in about 36.4 per cent of patients with miliary and meningeal tuberculosis. Considering that such examinations usually involve the sampling of 15 or 20 cc. of blood, of single specimens, the significance of these results are more impressive than the figures indicate. They give added support to the belief, now

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generally accepted, that a bacillaemia of greater or lesser degree accompanies nearly every form of tuberculosis, at some time or other.

There are three possible routes by which tubercle bacilli may invade the blood-stream: (*1*) by direct extension from a caseous lymph node along efferent lymphatics to the thoracic duct and thence into the venous circulation; (*2*) by settling first in the subintima of a blood vessel and producing an endangitis and then invading the blood-stream; (*3*) by rupture of a caseous focus directly into the lumen of a blood vessel. Arteries are believed to be more often eroded from without; veins are more apt to harbor intimal tubercles or thrombotic masses containing tubercle bacilli. In view of the multiplicity of morphological and clinical forms of the disease, it can be taken for granted that tubercle bacilli, on occasion, invade the blood-stream by any one of these channels. Under the best of conditions, however, it is difficult to determine the site of invasion. This becomes increasingly so with the passage of time in protracted disease.

The manner of ingress of tubercle bacilli into the blood-stream determines to some extent the course which the disease takes. Following the establishment of the primary complex, the dissemination of tubercle bacilli in the body, so-called "early generalization" takes place by direct propagation along lymphatic and venous channels. Since the primary infection may occur in adolescence or adulthood, the same mechanism applies in the production of early generalization of the disease in these age groups. In the vast majority of individuals this form of bacillaemia is of an abortive nature and does not produce clinically demonstrable disease. Occasionally, secondary factors such as the physiological state of the individual, the season of the year or the recent presence of diseases, such as measles and influenza, may modify the course of events and provoke a generalized and acute miliary tuberculosis.

Repeated haematogenous seedings of tubercle bacilli may give rise to a chronic miliary tuberculosis of protracted nature, depending to some extent on the time elapsing between successive implantations of tubercle bacilli. As might be expected, the resulting clinical phenomena assume varied and often bizarre forms. This type of haematogenous tuberculosis is best explained by assuming that somewhere in the body a caseous focus is present from which periodically tubercle bacilli pass into the blood-stream, probably along lymph channels. It is conceivable that, in such instances, the nidus contains few or attenuated forms of tubercle bacilli and that the amount of tuberculotoxin entering the circu-

lation as well as the receptivity of the host vary from time to time. This would explain the unevenness in the course of the disease.

Wide-spread dissemination of tubercle bacilli, occurring long after the primary infection, causes an acute miliary tuberculosis with milia of approximately the same size uniformly distributed throughout the body. The condition results from a sudden expulsion of a large amount of material into the blood-stream, as might occur when a lymph node ruptures into a large blood vessel. The acuity of the symptoms and the usually fatal outcome speak for a single and overwhelming superinfection. It has been suggested by Huebschmann (8) that tubercle bacilli might be capable of multiplying in the blood-stream as is true of other agents of septicaemia. Occasionally the miliary tubercles either become absorbed or remain latent. In the latter event, the clinical picture may resemble that of protracted haematogenous tuberculosis because the tuberculous foci in the various organs affected come to light at different times. For this reason, it is difficult to make a sharp distinction between the several forms of haematogenous tuberculosis on the basis of single or multiple seedings. An acute and terminating miliary tuberculosis is frequent in all forms.

Space does not permit a more extended discussion of the pathogenesis of haematogenous tuberculosis. Much of the literature on the subject is speculative because of the difficulty in tracing in specific instances the manner of ingress of the tubercle bacilli into the blood-stream. The mechanism involves labile phenomena, the initial stages of which are seldom ascertainable at the postmortem table. Indeed, if examination of the viscera is made weeks or months after the onset of the disease, as is usually the case, the pathologist may be hard pressed to differentiate the cause from the effect.

The site where the tubercle bacilli enter the circulation determines the extent of the haematogenous seedings in the various organs of the body and the clinical pattern which the disease assumes. The entry of tubercle bacilli into the thoracic duct or into a large neck vein results in a dominantly pulmonary form of haematogenous tuberculosis, by way of the right side of the heart. If secondary branches of the pulmonary artery are involved, the seeding may be limited to one lung or even a single lobe. Since the lungs filter the blood from the greater as well as the lesser circulations, it is readily understandable why this organ is so often the seat of haematogenous foci. Depending on the number of tubercle bacilli which are able to traverse the capillaries of the lung

into the pulmonary veins to the left side of the heart, there is a corresponding degree of seeding of other organs of the body. In health there is no anatomical anastomosis between the pulmonary and bronchial arteries so that, under certain conditions, the haematogenous seedings may remain limited to the lungs. The invasion of tubercle bacilli into the aorta or other large artery results in a generalized haematogenous tuberculosis with dominant localization in the visceral organs such as the spleen, liver and kidneys, producing, at times, the so-called typhoid form of the disease. The entry of tubercle bacilli into a pulmonary vein, a frequent site of invasion, results in a generalized miliary tuberculosis which often involves the meninges. The meninges may be involved if the site of rupture is in the aorta proximal to its bifurcation into the innominate and left common carotid arteries or by direct extension from caries of the spine or from activation of a latent tuberculous focus in the subarachnoid space. Localized forms of haematogenous tuberculosis result from tubercle bacilli gaining access to smaller radicles of the venous, arterial or lymphatic channels.

Haematogenous tuberculosis may appear in various morphological forms: the classical miliary tubercle, necrotic foci simulating small abscesses, large tuberculomata simulating neoplasms and in the lungs as a miliary caseous disease or bronchopneumonic infiltrations of considerable size not at all suggestive of a haematogenous origin. There is no adequate explanation for these variants aside from the character of the infection, the organ invaded, the site of invasion and to a great extent the patient's sensitivity to tuberculoprotein.

There is considerable diversity in the manner of evolution of these tuberculous deposits. In the lung which mirrors on the roentgen film the probable course of events in deeper organs, with due regard to anatomical differences, haematogenous tuberculous foci may undergo absorption or cavitation or they may remain in an indolent state for years. In each patient the disease tends to follow a recognizable pattern which expresses itself either as miliary tubercles, multiple tuberculomata, rapidly caseating foci or other manifestations. This is particularly true at the onset of the disease. Because of the unique position which the lungs occupy, atypical and transitional stages occur most often in these organs. Once bronchial ulceration takes place and tubercle bacilli invade these channels, the course of events becomes unpredictable. In some instances the disease progresses by way of the bronchi, larynx and intestines. In many, there is still evident a decided tendency for ex-

tension by the blood-stream. In the latter event, however, it is not always clear whether one is dealing with a new dissemination or the cropping out of haematogenous foci already in existence.

MORPHOLOGY OF HAEMATOGENOUS TUBERCULOSIS

The following pages will be devoted to a discussion of a number of forms of generalized haematogenous tuberculosis seen in the adult with special reference to pulmonary localization. Endogenous pulmonary tuberculosis arising from circumscribed haematogenous foci and spreading by way of the bronchi will not be considered here. The grouping of cases listed below will serve as a guide to the various manifestations of haematogenous tuberculosis to be described. It is not intended as a classiffication since, obviously, such is not possible of a disease in flux. The various forms of haematogenous tuberculosis are as fluid as the medium which gives rise to them.

Generalized Haematogenous Tuberculosis

A. Acute and Subacute Miliary Tuberculosis
   1. Septic form—Case 1
   2. Typhoid form—Case 2
   3. Meningeal form—Case 3
   4. With dominant pulmonary localization—Case 4
   5. With dominant throat localization—Case 5
   6. With dominant intestinal localization—Case 6
   7. Healing of generalized miliary tuberculosis—Case 7

B. Chronic Miliary Tuberculosis
   1. Protracted course
      a. Death due to hypertension and uraemia—Case 8
      b. Death due to acute miliary tuberculosis involving the meninges—Case 9
   2. Predilection for serous membranes
      a. Cortico-pleural localization—Case 10
      b. Polyserositis—Case 11
   3. Bizarre morphological forms
      a. Noncaseating tuberculosis—Case 12
      b. Recurring, round infiltrates—Case 13

C. Circumscribed Pulmonary Lesions in the Course of Generalized Haematogenous Tuberculosis
   1. Abortive, apical calcifications: "surgical tuberculosis"
   2. Subapical, exudative infiltration—Case 14

A word of explanation is in order regarding the type of material which forms the basis of this study. With few exceptions, patients entering Montefiore Hospital have been ill for some time, either at home or in another institution waiting for a bed in the Hospital. As a result, the very acute forms of haematogenous tuberculosis are seldom

admitted to the Hospital. The writer has had opportunities to observe such instances on the wards of the Morrisania City Hospital. In the instances cited, the disease was considered acute or subacute if it was continuously progressive. On the average, the duration of the disease in such cases or, more correctly, the final episode ranged from three to six months. The majority of the patients had protracted forms of haematogenous tuberculosis dating many years. To conserve space, illustrations will be presented only to clarify the subject matter. At best, reduced photographs of films are inadequate for the demonstration of miliary tuberculosis.

GENERALIZED HAEMATOGENOUS TUBERCULOSIS

The presenting symptoms of generalized haematogenous tuberculosis may be referred to any part of the body, the lymph nodes, the eyes, the skin, the lungs and pleura, the abdominal organs, the skeletal or the urogenital systems. For many months a tuberculous process involving any of these organs may constitute the only recognizable evidence of the disease. This is particularly true of the chronic forms of haematogenous tuberculosis. Acute and subacute forms of the disease are more apt to involve a number of organs at an early date as part of a systemic bacillaemia.

A. Acute and Subacute Miliary Tuberculosis

1. *Septic form:* This is a rare manifestation of haematogenous tuberculosis characterized by multiple, small and large abscess formations in various parts of the body. From outward appearances, the abscesses are not unlike those caused by pyemic infections. At times, the larger nodules, before undergoing liquefaction and necrosis, resemble tumor masses, particularly when present in the spleen, liver or lymph nodes. It is only on microscopical examination of the tissues or the finding of tubercle bacilli that the true nature of the condition is recognized. It has been suggested that this form of tuberculosis sepsis may be caused by an avian form of tubercle bacillus. The reader is referred to a comprehensive review of the subject in an article by Dugge (3).

The clinical course of the disease is acute and fatal. Some of the outstanding features of the condition are illustrated by the following instance which was observed recently on the wards of the Montefiore Hospital.

Case 1: K. K., 22, admitted to the Montefiore Country Sanatorium June 15, 1936; died January 4, 1938. Eighteen months before admission the patient changed her diet and reduced her weight from 185 to 145 lbs. This was done in an effort to cure the joint pains which she had had for a year. Later, she developed fever, chills and sweats and was told she had pulmonary tuberculosis. Examination revealed a minimal exudative lesion in the left upper lobe which remained unchanged throughout her sanatorium stay. No tubercule bacilli were found in the sputum. The red blood cells showed an increased sedimentation velocity. Because of persistent complaints of joint pains, a gonorrheal complement fixation test was done and was reported positive. In March, 1937, she developed fever to 103°F. and became acutely ill, the chief complaints being generalized joint pains. She was transferred to the Montefiore Hospital.

Physical examination revealed a well nourished young woman. The lymph nodes in the left axilla were moderately enlarged. An X-ray film of the chest revealed no change in the infiltrations in the left upper lobe. A month later the fever became higher and she developed tenderness in the lower abdomen. The spleen was palpable. Soon the right knee became swollen, red and tender. A film of the knee joint revealed an area of rarefaction in the lower end of the femur. Films of the chest (figure 1) revealed progression of the area of infiltration in the left upper lobe and, in addition, fresh exudative infiltrations in the right lung. Repeated search for tubercle bacilli in the sputum and pus obtained from the knee joint, which had by this time undergone abscess formation, failed to reveal the organism. The patient died in coma following a period of anuria.

Postmortem examination, performed by Dr. S. Biller, revealed small abscess formations in various organs of the body. The infiltrations in the left upper lobe consisted of a collection of small, yellow abscesses in consolidated lung tissue (figure 2). There were no cavities suggestive of tuberculosis. Multiple, subacute abscesses were scattered in the other lobes. The abscesses consisted of discrete areas of consolidation with central liquefaction. They did not have the appearance of tuberculosis. Histological examination of the tissues at the edge of these abscesses revealed tuberculous granulation tissue. Small abscesses such as those found in the lungs were present in the spleen, liver and mesenteric lymph nodes. A subacute osteomyelitis of the right femur had undergone abscess formation and had ruptured into the right knee joint with resulting cellulitis. A ruptured splenic abscess caused peritonitis.

An interesting feature of the bacteriological investigations in this case were the large acid-fast, rod-shaped bacteria, many of them beaded, seen in the sections of the lung, liver, spleen and mesenteric lymph nodes. The visceral

FIG. 1

FIG. 2

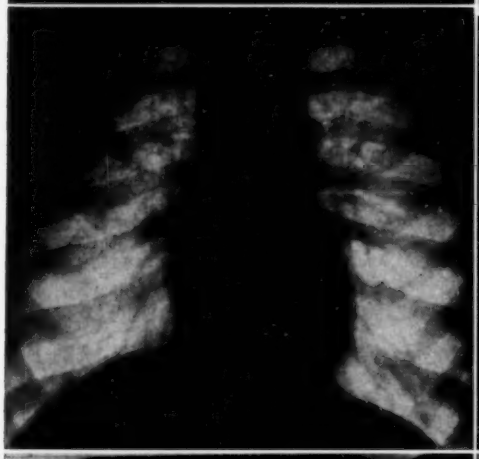

FIG. 3

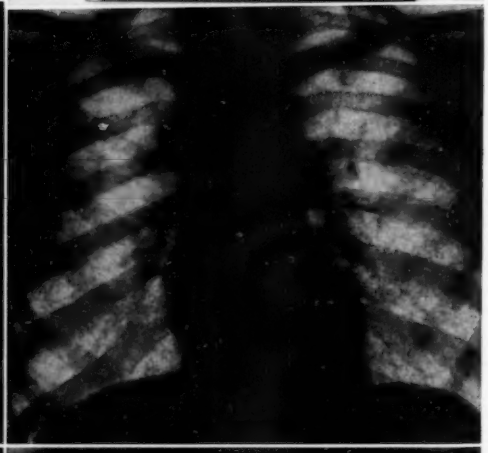

FIG. 4

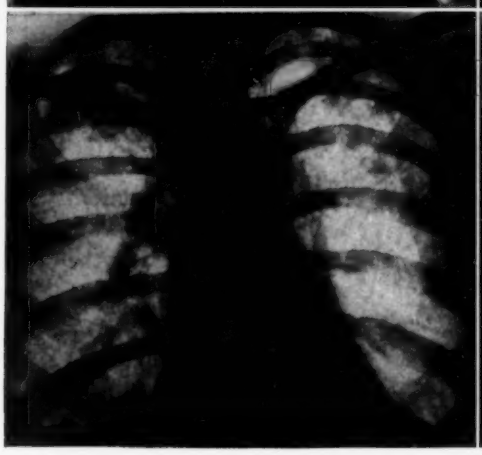

FIG. 5

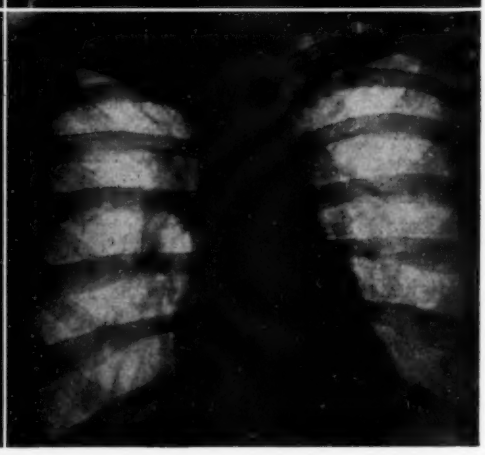

FIG. 6

FIGS. 1-6

organs of guinea pigs injected with the material revealed identical forms of acid-fast organisms. Inoculations into rabbits gave negative results.

2. *Typhoid form:* Haematogenous tuberculosis affecting chiefly the abdominal organs may give rise to a clinical picture resembling closely that of typhoid or paratyphoid fever. Abdominal distress, vomiting, fever and prostration, a relatively low pulse, leucopenia, an enlarged spleen and even a rash in the skin may cause the physician to believe he is dealing with an enteric disease. A repeatedly negative Widal test as well as negative cultures for other organisms and, in time, the appearance of tubercles in the lung and other parts of the body lead to a correct diagnosis. It is interesting to note that even the Widal test may be positive in tuberculosis (9).

The following example is classical. It relates to a former occupational therapist of Montefiore Hospital who was admitted as a patient on a number of occasions over a period of eight years. In most patients, the typhoid form of haematogenous tuberculosis is apparently of short duration, probably because the patient comes under observation in the terminal stages of the disease. This is true in many other forms of haematogenous tuberculosis in the adult. The fact is often overlooked that the clinical story may be the final chapter of a protracted disease.

Case 2: F. R., 28, third and final admission to the Montefiore Hospital March 17, 1931; died July 9, 1931. In 1923, the patient was suddenly seized with pain in the right lower abdomen. She had no fever, no nausea and vomited once. She was admitted to the hospital where, after observation, the con-

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FIG. 1. K. K. November 16, 1937. Exudative infiltration in left upper lobe. Circumscribed nodules throughout right lung. Septic form of generalized haematogenous tuberculosis characterized by small and large abscess formations in visceral organs.

FIG. 2. K. K. Necropsy, January 4, 1938. Specimen of left lung. Abscess formations in consolidated upper lobe. Small abscesses in lower lobe. Similar lesions present in right lung, spleen, liver, lymph nodes, knee joint.

FIG. 3. H. T. September, 1928. Miliary and submiliary tubercles symmetrically distributed in upper halves of both lungs.

FIG. 4. H. T. February 16, 1929. Tubercles now present in the lower as well as the upper lobes. Enlargement of hilum lymph nodes. Necropsy, March 22, 1929, revealed generalized haematogenous tuberculosis.

FIG. 5. A. K. April 6, 1933. Miliary tubercles uniformly distributed in both lungs. Older lesions in apices. Tuberculous peritonitis accidentally discovered on laparotomy. Tuberculous granulation tissue removed from cervical endometrium and periapical (dental) tissue.

FIG. 6. A. K. February 25, 1938. Clearing of tubercles in the lungs. Fibroid changes in apical regions. In good health five years later.

dition was diagnosed as chronic appendicitis. She had a similar episode three years previously. In 1928, she was again confined to bed. She stated that she had abdominal discomfort in the intervening five years.

In March, 1931, she developed severe pain in the left chest, fever, chills and profuse sweats. On the second day of her admission to the hospital, fluid was discovered in the left pleural cavity. In spite of a fever ranging from 101° to 104°F., a leucocyte count on the third day of her hospitalization revealed 8,200 cells with 68 per cent polymorphs. Blood cultures were sterile. A blood Widal test for typhoid and paratyphoid was negative. She continued to have high fever; at times, she was irrational. Repeated films of the chest revealed some increase in the amount of fluid in the left pleural cavity. Later films showed a few nodular infiltrations in the right upper lobe. She died about four months after the onset of her last illness.

Postmortem examination, performed by Dr. C. Spark, revealed a generalized miliary tuberculosis with a pleural effusion in the left chest. Miliary tubercles were found throughout the lungs, peritoneum, spleen, small intestine, liver and kidneys. The lungs did not contain gross cavity formations. Of interest, in the light of the patient's previous history of supposedly appendiceal seizures, was the finding of a large, densely adherent spleen which could be separated from its attachments with great difficulty. The capsule of the spleen was thickened and studded with yellowish-gray tubercles.

3. *Meningeal form:* Involvement of the meninges in the adult is often a terminal event in the course of generalized haematogenous tuberculosis. It is seldom an early manifestation of the disease. Urogenital or osseous tuberculosis, or both, frequently coexist. The former complication, being more common in the male, accounts for the greater incidence of tuberculous meningitis in this sex. In infants and children, tuberculous meningitis is often the outstanding feature and occasionally the only demonstrable evidence of blood-stream invasion.

In an adult, a persistent and uncontrollable headache and a rise in temperature, occurring in the presence of urogenital or osseous tuberculosis, are almost pathognomonic of tuberculous meningitis. It is a good practice to look for evidence of urogenital tuberculosis when such symptoms appear. Classical findings such as projectile vomiting, convulsions or marked loss of weight often seen in children are uncommon in adults. In the adult, there is frequently noted a change in the individual's personality. This may take the form of abuse of his neighbor, throwing objects at attendants, gross uncleanliness, fondling the genitalia and other aberrant acts. As in children, one usually obtains neurological signs of cortical irritation and tubercle bacilli in the spinal

fluid. On the whole, tuberculous meningitis in the adult is less apt to conform to type than is the case in children. Occasionally, the meningeal syndrome is among the first clinical manifestations of haematogenous tuberculosis, as illustrated by the following instance.

Case 3: M. B., 27, admitted to the Montefiore Hospital February 1, 1929; died February 5, 1929. Seven weeks before admission, the patient developed weakness, cough, expectoration, night sweats and vomiting. After staying at the Montefiore Country Sanatorium for a month, he was transferred to the city institution having developed signs of generalized miliary tuberculosis and tuberculous meningitis. Neurological examination revealed rigidity of the neck, bilateral Kernig and other confirmatory signs of tuberculous meningitis. Spinal fluid contained tubercle bacilli. A film of the chest showed miliary nodules distributed throughout both lungs showing little evidence of fibrosis. He died four days after admission, the entire duration of his illness being about two months.

Postmortem examination, performed by Dr. S. Jacobson, revealed voluminous lungs with small and larger nodules throughout the parenchyma. No cavities were found. Tubercles were present in the spleen and kidneys. The brain was found to have a markedly thickened pia-arachnoid at the base extending and covering the optic tracts, the optic chiasm, the peduncles and the upper two-thirds of the pons. The right temporal lobe showed beginning destruction of the cortex. Microscopical examination confirmed the diagnosis of tuberculous meningitis with invasion of the brain substance.

4. *With dominant pulmonary localization:* It is noteworthy that, in patients with subacute miliary tuberculosis, films of the chest, taken at frequent intervals, reveal repeated localizations of tubercles in the lung. This phenomenon emphasizes the essentially undulant nature of the disease, a characteristic that finds its fullest expression in protracted forms of haematogenous tuberculosis. Depending on the tempo of the disease, repeated seedings of tubercle bacilli in the lungs of an individual hypersensitive to tuberculoprotein are apt to provoke severe constitutional and local disturbances manifested in fever, chills, sweats, cough, expectoration and blood-spitting. Haemoptysis, in such patients, is the result rather than the cause of the tubercle formations and the associated perifocal reactions. The cause and the effect of pulmonary haemorrhage are often confused because the initial film of the chest is usually taken after the occurrence of the bleeding. A later paper will deal with haematogenous forms of pulmonary tuberculosis with reference to the rôle played by the dual circulation in determining certain topographic features of the disease.

Case 4: H. T., 16, admitted to the Montefiore Hospital February 15, 1929; died March 22, 1929. At the age of 14, the patient developed painless swellings on both sides of the neck and in both inguinal regions. The lymphadenopathy was treated first by alpine lamp, but when the lymph nodes became larger they were incised. About a year later, the swellings recurred. Several films of the chest failed to reveal tuberculous changes.

In September, 1928, he suddenly developed chills and fever to 103°F. He coughed and, on several occasions, expectorated blood. A film of the chest at this time (figure 3) revealed many small tubercles in the upper halves of both lungs. He was admitted to the Montefiore Country Sanatorium and, after a month's stay, was transferred to the Hospital. Examination now revealed small tubercles diffusely scattered in the lower as well as the upper lobes (figure 4). In addition, the hilum lymph nodes were more prominent. The sputum did not contain tubercle bacilli on direct examinations. Shortly after admission to the Montefiore Hospital, the patient developed signs of tuberculous meningitis (rigidity of the neck, positive Kernig, tubercle bacilli in the spinal fluid) and died in coma.

Postmortem examination, performed by Dr. L. Hutner, revealed scattered in both lungs and pleura innumerable tubercles of varying size. There was no cavitation. Similar tubercles were found in the liver, spleen, intestines, pancreas, kidneys, prostate, seminal vesicles and suprarenals. There were enlarged tuberculous lymph nodes in the cervical, paratracheal and mediastinal regions. A tuberculous meningitis involved the pia-arachnoid at the base of the brain, spreading over the optic chiasm and extending between the temporal and parietal lobes.

5. *With dominant throat localization:* Not infrequently, haematogenous tuberculosis early involves the larynx and pharynx. There is usually symmetric involvement of the extrinsic parts of the larynx: the epiglottis, the arytenoepliglottic folds and the arytenoids. Oedema and widespread ulceration of the affected parts give rise to symptoms which dominate the clinical picture. The patient complains of hoarseness, pain in the throat and inability to swallow. Of all complaints associated with tuberculosis as a disease, the most trying ones are the excruciating pain in the throat and inability to swallow caused by ulcerative pharyngitis and laryngitis. It taxes the physician's skill to bring relief. At the onset of the disease, because of the comparative paucity of symptoms referable to the chest, the patient is apt to consult a throat specialist who, without the aid of a film, may diagnose and treat the condition as a primary disease. This has happened to quite a number of our patients, as the following instance illustrates.

Case 5: R. D., 25, admitted to the Montefiore Hospital June 16, 1933; died July 5, 1933. Six months following the birth of her child, in 1929, the patient developed increasing hoarseness associated with slight cough and expectoration. She was told by a physician she had tuberculous laryngitis but no active pulmonary tuberculosis. A film of the chest was not made. Under local treatment the hoarseness improved but later there were recurrences of symptoms. In February, 1933, the hoarseness returned in aggravated form. At this time, she also developed fever, lost weight and had dyspnoea on exertion.

Four months later, examination at the Montefiore Hospital revealed superficial, irregular ulcerations over both tonsils, pillars and soft palate. One-half of the epiglottis was eroded; the remainder had irregular ulcerations which extended over both arytenoids and cords. A film of the chest revealed innumerable small tubercles evenly distributed in both lungs, those in the upper lobes showing evidences of fibrosis. The sputum contained tubercle bacilli. The patient's fever ranged from 101° to 104°F. She complained of severe pain in the throat which was not relieved by alcohol block of the superior laryngeal nerves. She died three weeks after admission to the hospital.

Postmortem examination, performed by Dr. M. Krinsky, revealed extensive ulcerations of the larynx, pharynx, epiglottis and base of the tongue. Both lungs were seeded with miliary tubercles, the upper lobes containing thin-walled, noncommunicating cavities. Areas of caseation and miliary tubercles were present in the left kidney, ureter, bladder, cervix uteri, intestines, appendix, liver and spleen.

6. *With dominant intestinal localization:* Tuberculosis of the intestines occurs, as a rule, as a late manifestation of cavitary pulmonary tuberculosis. Direct infection by tubercle bacilli swallowed in the sputum is the commonly accepted cause. Nonspecific factors are also believed to play a part. Occasionally, the intestines are involved as part of a haematogenous disease. In either event, the ileocaecal region is the favorite site of localization of the infection. Large segments of the mucosa of the bowel may be denuded by superficial and deep ulcers, local extension taking place by way of the lymphatics within the mucous membrane and to the serosa. Penetration may occur at the base of an ulcer and cause peritonitis. Considering the wide extent of the process in most patients, it is remarkable that perforation does not occur more frequently. In the instances of ruptured tuberculous ulcers which have come to the writer's attention, there were often present additional exciting elements such as constriction of the bowel by scar formation of partially healed ulcers or peritoneal bands induced by previous operative procedures. In a few instances, the presence of large, caseating mesen-

teric lymph nodes suggested the possibility that perforation of the gut might have occurred from without.

The following instance is of unusual interest. It illustrates the condition of haematogenous intestinal tuberculosis in a patient with unilobar miliary pulmonary tuberculosis. The miliary tubercles found at necropsy in the remainder of the lungs and in the spleen were of a terminal nature. During life, repeated films of the chest revealed small nodular infiltrations confined to the left upper lobe.

Case 6: M. G., 21, admitted to the Montefiore Hospital December 26, 1933; died April 7, 1934. Three years previously, the patient had a pleural effusion on the left side and 300 cc. of straw-colored fluid were removed. He recovered and returned to work. He was well until May, 1933 when he developed a nonproductive cough and gradual loss of weight. Tuberculosis was discovered in the left lung and he entered the Montefiore Country Sanatorium. Examination revealed miliary tuberculosis with small and moderately large infiltrations limited to the left upper lobe. Shortly after admission, he began to have diarrhoea, fever and colic which were ascribed to intestinal tuberculosis. He was transferred to the Montefiore Hospital. Films of the chest showed no change in the pulmonary disease. Examinations of the sputum failed to reveal tubercle bacilli; they had been found on one occasion at the Sanatorium. In addition to the marked abdominal distress, the patient developed symptoms of toxaemia, jaundice and died.

Postmortem examination, performed by Dr. S. Smith, revealed caseous and conglomerate tubercles of varying size in the left upper lobe. No cavities were seen grossly. Innumerable pin-point tubercles were scattered in the other lobes and in the spleen, apparently the result of a terminal miliary dissemination. The hilum lymph nodes were small and anthracotic. Extensive ulcerations, some older but the majority recent, were present in the jejunum, ileum, caecum and ascending colon. In parts of the gut very little normal appearing mucosa could be seen. At one point, near the ileocaecal valve, an ulcer had ruptured causing acute, fibrinopurulent peritonitis, particularly marked in the pelvic region. The peritoneal cavity contained about 1,000 cc. of yellowish liquid containing faecal matter.

7. *Healing of generalized miliary tuberculosis:* That miliary and large tubercle formations can heal by fibrosis and calcification is a matter of common knowledge. Less known, however, is the fact that wide-spread miliary tuberculosis may heal to an extent that pathological changes may not be demonstrable either clinically or, in the few instances studied, at necropsy. Healing by absorption of wide-spread

miliary tuberculosis has been reported by a number of observers. This happy event occurred in the following patient who has been under continuous observation in the Montefiore Hospital and in the Tuberculosis Clinic for the past five years.

Case 7: A. K., 35, admitted to the Morrisania City Hospital November 29, 1932; transferred to the Montefiore Hospital April 5, 1933; discharged to the Tuberculosis Clinic July 11, 1933. Ten years previously, at the age of 25, the patient developed a pleurisy in the left chest and was confined to bed for ten weeks. She remained in good health until February, 1932, when she delivered a child. The day following delivery she had fever, cough and soon developed abdominal cramps and loose, watery stools. On one occasion she spat up blood. The symptoms slowly improved. In November, 1932, she noted enlargement of the abdomen associated with weakness and loss of weight.

The patient was admitted to the Morrisania City Hospital for repair of a prolapsed uterus. At operation, performed on December 16, 1932, the peritoneal cavity was found studded by innumerable small tubercles. No free fluid or adhesions were present. Both tubes were enlarged to about three times the normal thickness and were nodular. No intraäbdominal procedures were performed. The abdomen was inflated with oxygen and closed. The wound healed well. At this time, a film of the chest revealed extensive miliary infiltrations in both lungs. Histological examination of the cervical endometrium revealed the glands to be of normal appearance but the stroma studded with numerous tubercles.

On admission to the Montefiore Hospital, in April, 1933, there were still visible throughout all the lobes numerous, small, discrete tubercles averaging about the size of a match-head. Older lesions were present in the apices (figure 5). While at the hospital she was treated in the Dental Department. Examination of a specimen of periapical tissue showed tuberculous granulation tissue with typical tubercles consisting of epithelioid cells, giant cells and lymphocytes. The sputum, at no time, revealed tubercle bacilli. The patient did very well and was discharged three months later. Films of the chest taken periodically have revealed a gradual disappearance of the tubercles in the lungs. The clearing was evident in the early months of 1934 and was complete in the fall of 1935. A recent film is reproduced (figure 6). She attends to her household duties and feels well.

B. Chronic Miliary Tuberculosis

This form of haematogenous tuberculosis is characterized by an insidious onset and a slow, relatively benign evolution. In contrast to the wide-spread distribution of tubercles, the symptoms are mild

and the physical findings few and of little value in furnishing an index to the extent of the disease. The discovery of this form of tuberculosis is often accidental. In the lungs, chronic miliary tuberculosis has a roentgen appearance which, although resembling the acute form in the extent of the distribution of the tubercles, shows the latter to be of considerable duration. In other parts of the body, unless there are gross involvements, the extent of the disease can be ascertained only at necropsy. However, some inkling of its wide-spread nature is obtainable from the history, clinical and roentgen findings. The tendency for fibrosis of individual tubercles depicted on the film is also manifest in the visceral organs. Fibrotic and, at times, calcific tubercles are found in the spleen, liver, kidneys and other organs, occasionally in the same stage of development and apparently the result of a single haematogenous dissemination. More often, the tubercles are of various gradations in size and age and almost invariably there are interspersed freshly formed tubercles, the result of a recent spread of the disease. Because of the tendency for episodic haematogenous seedings, a clinical distinction between chronic and arrested miliary tuberculosis is not feasible.

On physical examination of the chest, one elicits signs of apical sclerosis with dulness and harsh breath sounds in both upper lobes. Râles are few or absent and when audible are dry and found mainly at the bases of the lungs. The physical findings may remain unchanged from year to year unless bronchial ulceration takes place. Examination of the abdomen may reveal an enlarged spleen. From the frequency with which splenomegaly is encountered in patients with chronic miliary tuberculosis, its presence is of diagnostic value. In patients suspected of having chronic miliary tuberculosis, roentgen films of the abdomen may reveal calcifications in the spleen. The many negative films, however, hardly pay for the effort of trying to locate them. A number of instances have been reported where the spleen was extirpated in the mistaken belief that the condition was Banti's disease. One of our patients, not included in the case reports cited, had a markedly enlarged spleen, but, in the presence of tuberculosis of both breasts and the right knee and from the characteristic roentgen appearance of the lungs, the diagnosis was not in doubt. This was confirmed by biopsy of a lymph node. On admission to the Montefiore Hospital, however, this patient had a leucocyte count, on one occasion, as low as 5,050 (others were slightly higher) and a red cell count of 7,400,000. Banti's disease was diagnosed until disproved by the findings mentioned previously.

Grethmann (4) has commented on the multiplex picture occasionally observed in acute and subacute forms of haematogenous tuberculosis particularly in the pigmented races. In our experience, this characteristic is also quite pronounced in white patients with chronic haematogenous disease. The complex nature of chronic miliary tuberculosis, its protracted course, its predilection for serous membranes, its pleomorphism, its localization in organs (breasts, skin, eyes, salivary glands, glands of internal secretion, small bones) seldom involved in ordinary forms of tuberculosis will be best illustrated by selected case reports.

1A. *Protracted course; death due to hypertension and uraemia:*

Case 8: A. G., 33, admitted to the Montefiore Hospital May 10, 1927; discharged June 24, 1927; died October 12, 1935. Four years before admission to the Montefiore Hospital, the patient developed *lupus erythematosus* of the face and glandular swellings at the neck. The condition cleared up under radiotherapy. Five months before admission, the patient developed cough and pain in the chest accompanied by fever, night sweats and weakness. She entered a hospital where tuberculous lymph nodes were found in the right axilla, miliary tuberculosis in both lungs and a left-sided pleural effusion.

At the Montefiore Hospital, in addition to the diffuse miliary tuberculosis in both lungs, a large mass was discovered in the right breast which in time ulcerated, the pus containing tubercle bacilli. A similar lump developed in the left breast which also ulcerated and discharged pus. In time, the ulcers healed. Tubercle bacilli were not found in the sputum. The blood pressure was 120/70; urea nitrogen 13.4 mg. The patient felt well, had no fever, gained weight and was discharged from the hospital six weeks after admission.

A film of the chest taken a year later showed no change in the distribution and numbers of the small tubercles in both lungs. The patient was under observation of the writer during the following eight years without noteworthy change in her condition. In the summer of 1935, she began complaining of headaches. In the fall, her blood pressure registered 230/110. The urine contained a heavy trace of albumin and casts. Urea nitrogen was 49. mg. There was papilloedema with loss of vision in the right eye. The patient developed periods of amnesia and died shortly thereafter in uraemia. A postmortem examination was not made.

1B. *Protracted course; death due to acute miliary tuberculosis involving the meninges:*

Case 9: I. E., 56, admitted to the Montefiore Hospital January 15, 1931; died August 13, 1931. At the age of 16, the patient had draining sinuses in the right groin which in time healed. Three years before admission to the

hospital, he developed a tumor mass over the right anterior aspect of the chest. The mass was excised but the wound did not heal and several discharging sinuses developed at the site of operation. The patient stated that in the preceding ten years he had been losing weight and strength but had few symptoms referable to the lungs.

Examination revealed a number of draining sinuses over the right lower chest and tuberculous osteomyelitis of the lower ribs. A film of the chest showed fibrotic tuberculosis in both upper lobes with a moderate number of calcific tubercles scattered throughout the parenchyma. There was some thickening of the pleura on the right side. The sputum, at first, contained no tubercle bacilli. Later, bacilli were found. A week following admission, he developed a painless swelling in the left scrotum. This was found to be part of a urogenital tract tuberculosis. Five months after admission, he developed signs of cortical irritation. At the same time, a film of the chest revealed an acute miliary tuberculosis of the lungs superimposed on the older process. He died two months later.

Postmortem examination, performed by Dr. C. Spark, revealed fibronodular tuberculosis in both upper lobes with some degree of bronchiectasis. The remainder of both lungs were seeded with recent miliary tubercles. No distinct cavitation was apparent. The hilum lymph nodes were enlarged and calcific. In addition, there was present a tuberculous periostitis of the eighth, ninth and tenth ribs with sinuses in the right anterior chest wall. Extensive tuberculosis, showing considerable chronicity, involved the seminal vesicles, testes, epididymes and middle lobe of the prostate. Multiple tuberculomata were found in the left suprarenal gland and in the brain.

2. *Predilection for serous membranes:* The tendency for haematogenous tuberculosis to involve the serous membranes of the body is revealed in the case reports cited and in the many more which for lack of space are not included. Of the larger serous membranes, the meninges, peritoneum, pericardium and the pleura, the last mentioned is the one most often involved. Many patients with pulmonary tuberculosis trace the onset of their disease to a pleurisy with or without demonstrable effusion. The reason for the frequent involvement of the pleura is not difficult to understand. Aerogenous as well as haematogenous localizations of tuberculosis occur in the subpleural layers of the lung either in the neighborhood of an interlobar fissure or the general pleural cavity. The anatomical arrangement of the blood and lymph supply of the serous and subserous layers of the lung is chiefly responsible for the subpleural deposition of tubercles. The favorite site for such tubercles, as shown by Miller (15), is in the transitional

zone from the bronchial to the pulmonary circulation. The bronchial artery supplies the pleura. The pulmonary artery supplies the subpleural lymphoid tissues. Tubercle bacilli are thus able to travel by way of the superficial (pleural) or deep (pulmonary) lymphatics to the surface as well as within the parenchyma of the lung. This is the reason why pulmonary tuberculosis resulting from implantations by way of the blood-stream is particularly prone to be associated with a pleural reaction.

2A. *Cortico-pleural localization:* A striking example of the rôle played by the pleura as a starting point of tubercle formation is shown in the following instance of so-called "cortico-pleural" tuberculosis, described by Pagel (16) and more recently by Stefko (20). The distribution of tubercles along the margins of the lung and individual lobes is rarely encountered at the postmortem table for the reason that the condition is probably an intermediary stage of the disease. Recurring haematogenous seedings involve in time the inner parts of the lung and obscure the onset of the lesions. The unusual prominence of the lymph vessels in the lungs of the following patient indicates a tendency for lymphogenous extension at this stage of the disease.

Case 10: L. C., 22, admitted to the Montefiore Country Sanatorium August 2, 1937; transferred to the Montefiore Hospital February 7, 1938; died April 20, 1938. In the fall of 1936 the patient developed cough, expectoration, listlessness, pain in the chest and later dyspnoea. She was examined in a hospital where a film of the chest is reported as revealing tent-like basal adhesions over the right diaphragm and numerous soft densities scattered in both lungs. She was admitted to the Montefiore Country Sanatorium where films of the chest revealed bilateral haematogenous tuberculosis with areas of breaking-down in the upper lobes. The sputum contained tubercle bacilli. For a time she felt well but soon developed fever, an increase in cough and expectoration and pain in the lower abdomen, associated with cramps and diarrhoea. At the hospital, films of the lungs revealed an increase in the miliary seedings (figure 7). Films of the gastrointestinal tract confirmed the clinical impression of the presence of intestinal tuberculosis. The finding of tubercle bacilli in the urine indicated the existence of urogenital tuberculosis. She died in April, 1938.

Postmortem examination, performed by Dr. H. Agatston, revealed the parenchyma of both lungs occupied by discrete and confluent tubercles with cavities in the upper lobes. A distinctive feature was the nature of the distribution of the tubercles. They were very prominent along the margin for a width of 2 cm., as a well demarcated border. Within this border of tubercles

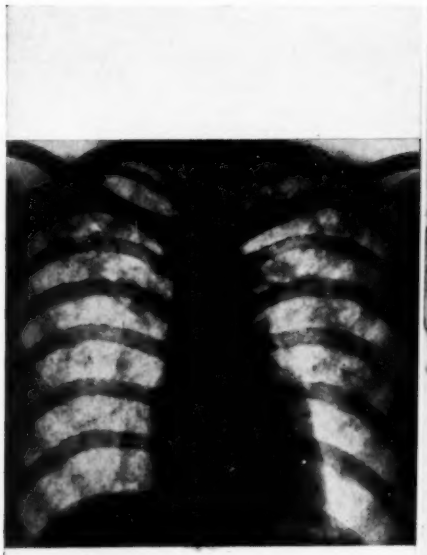

FIG. 7

FIG. 8

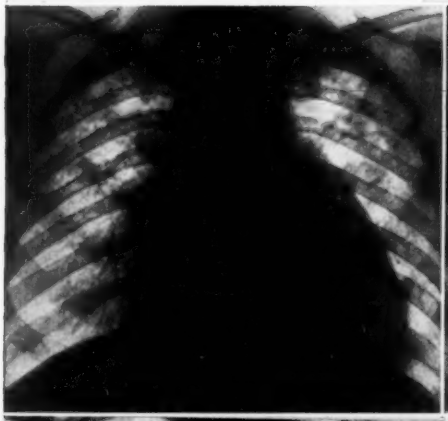

FIG. 9

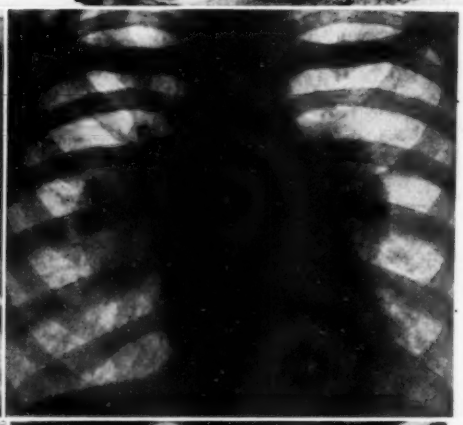

FIG. 10

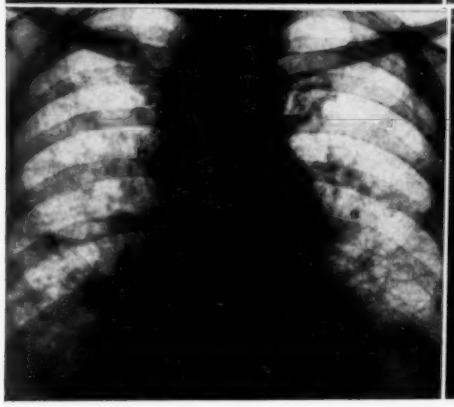

FIG. 11

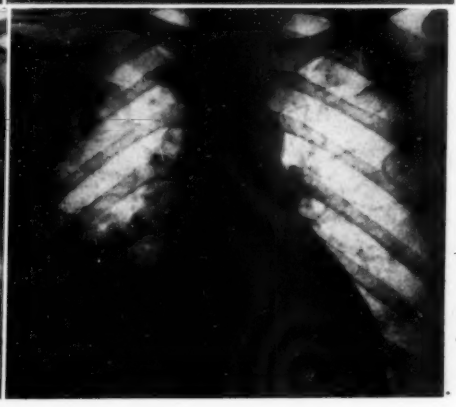

FIG. 12

FIGS. 7–12

there were present numerous dilated bronchioles. The lymphatic vessels along the border were thrown into relief in the form of a delicate, lace-like pattern (figure 8).

In addition to the lung findings, the jejunum, caecum and ascending colon contained large, shallow ulcers. The serosal surface of the gut was densely studded by small, raised, whitish tubercles. The ovaries were enlarged, soft and partially replaced by large caseous masses which involved the tubes. The endometrium of the uterus was uniformly covered with a layer of friable caseous material. No abnormalities were found in the brain and spinal cord.

2B. *Polyserositis:* Serous membrane tuberculosis occurs not only as an accompaniment of organic disease but occasionally as a distinct entity. The condition may assume the form of a rudimentary polyserositis, as pointed out by Mayrhofer (14), in association with fleeting infiltrations in the lung, certain skin lesions, polyarthritis, lymphadenopathies and other manifestations of tuberculous bacillaemia whose true nature is recognized late in the disease or only at necropsy. The writer recently had occasion to see the organs of a patient who presented this form of haematogenous tuberculosis. The patient, a girl of twenty, was treated on the Medical Service of the Montefiore Hospital for a presumably rheumatic heart disease. Her illness began ten years previously when, shortly following the development of cervical adenitis which had to be aspirated, she began to experience pains in the joints. During her long illness which was dominated by symptoms of polyarthritis, she had pleuritis, pericarditis and on occasion was suspected of having peritonitis. These findings were ascribed to the rheumatic state. It is noteworthy, however, that, in spite of intermittent

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FIG. 7. L. C. February 8, 1938. Uneven densities and miliary tubercles in both lungs.

FIG. 8. L. C. Necropsy, April 20, 1938. Specimen of left lung showing cortico-pleural localization of tubercles. Tuberculosis of intestines, ovaries and uterus.

FIG. 9. M. G. March 22, 1927. Marked enlargement of cardiac shadow. Nodular tuberculosis in both lungs. Necropsy, December 6, 1928, confirmed diagnosis of polyserositis (pericardium, pleura, peritoneum) and generalized haematogenous tuberculosis.

FIG. 10. M. de F. March 18, 1938. Marked enlargement of hilum lymph nodes with fine infiltrations radiating into lung parenchyma. Instance of noncaseating tuberculosis presenting uveoparotid syndrome. Biopsy of lymph node revealed Boeck's sarcoid.

FIG. 11. B. G. April 28, 1938. Enlarged hilum lymph nodes. Stippled infiltrations extending into the lung, particularly in lower halves, simulating lymphangitic carcinoma. Instance of noncaseating tuberculosis presenting uveoparotid syndrome. Biopsy of lymph node revealed structures of Boeck's sarcoid.

FIG. 12. A. M. May 7, 1938. Isolated, round infiltrations with central necrosis, recurring over a period of five years. Tuberculous iridocyclitis. Polyarthritis.

chills and fever, repeated blood counts revealed a relative leucopenia with a high percentage of lymphocytes. About a month before exitus, infiltrations were noted in the lungs for the first time on roentgen examination. Necropsy revealed a generalized miliary tuberculosis and tuberculous pericarditis.

Frank forms of tuberculous polyserositis, presenting the Pick syndrome, are comparatively rare. A classical example is the following.

Case 11: M. G., aged 23, admitted to the Montefiore Hospital February 23, 1927; died December 6, 1928. The history dated about two years with the onset of cough, night sweats, pain in the chest, weakness and loss of 25 lbs. in weight. On one occasion, he spat up blood. Shortly before admission to the Montefiore Hospital, the patient developed increasing dyspnoea and abdominal cramps.

Examination revealed nodular tuberculosis in both lungs with evidences of pleural effusions at the bases which quickly absorbed. The heart was markedly enlarged (figure 9). The sputum contained tubercle bacilli. The red cell count was 5,300,000 and the haemoglobin 83 per cent. There was soon noted enlargement of the liver (verified by pneumoperitoneum). Fluid was found in the abdomen containing lymphocytes but no organisms. Toward the end of his life, the patient developed fever, convulsions and other neurological manifestations which were ascribed to tuberculomata of the brain.

Postmortem examination, performed by Dr. S. Jacobson, revealed diffuse nodular tuberculosis in both lungs, some pin-head in size, others larger. In the upper lobes were small caseous areas. In addition, miliary tubercles were found in the liver, kidneys, pancreas, prostate, seminal vesicles and parathyroid. There were scattered small ulcers in the colon, probably of nonspecific origin. The heart could not be removed from the lungs. Both organs as well as the visceral and parietal layers of the pleura were inseparable by a diffuse tuberculous pleuritis and pericarditis. The abdomen contained 700 cc. of milky, yellowish fluid and diffuse fibrous adhesions which bound the abdominal viscera to one another and to the abdominal wall. The liver was cirrhotic and weighed 2,700 g. The spleen weighed 1,020 g. From the presence of tuberculomata in the suprarenals it was suspected that the cerebral symptoms were due to the same cause, the brain not being obtainable for examination.

3A. *Bizarre morphological forms; noncaseating tuberculosis:* In 1899, Boeck (2) described a condition of disseminated papular nodules in the skin characterized histologically by tubercle-like structures composed of epithelioid cells, small numbers of lymphocytes and rare giant cells. In the instance cited, there was associated swelling of the lymph nodes

which, according to Boeck, could be described as perivascular sarcomatoid tissue. In time, Boeck's sarcoid was found to be a generalized disease, referred to by some writers as sarcoidosis (13) and associated with other conditions of equally obscure origin such as cystoid formations in small bones (Jüngling (11)) and uveoparotid fever (Heerfordt (6)).

Schaumann's (19) studies, and recently those of Pinner (17), have directed particular attention to the probable tuberculous aetiology of the disease, designated by the former as benign lymphogranulomatosis and by the latter as noncaseating tuberculosis. These descriptives characterize the condition. It is a generalized disease of the reticuloendothelial system affecting particularly lymph structures but also the spleen, liver, skin, eyes, bones, lungs, salivary glands and the nervous system. Outstanding features are an absence or paucity of caseation, usually an absence of acid-fast bacilli and a histological structure such as that described by Boeck. Noteworthy about the condition, as pointed out by Sulzberger (21) and noted by most observers, is a low and often complete absence of sensitivity to tuberculin. Death is usually due to the development of progressive pulmonary tuberculosis or cardiac failure. Pinner's (17) article contains a complete review of the literature on the subject.

The three instances of noncaseating tuberculosis which have come to the writer's observation in the past two years took the form of uveoparotid fever. The diagnosis was confirmed by histological examination of lymph nodes in two instances; of a lymph node and tissue from the iris in the third. A brief description will be given of one patient because the chest findings (present in all three) are unusually instructive.

Case 12: M. de F., colored, 18, admitted to the Morrisania City Hospital on four occasions; in 1934 when she delivered a child; in 1935 for a second delivery; in 1936 for incision and drainage of a breast abscess; and in November, 1937. Of interest in her past history is the fact that her father and mother died from tuberculosis and that in 1930, at the age of 11, the patient spent eight months in a tuberculosis institution. A report states that on October 23, 1930 a film of the chest revealed marked enlargement of the paratracheal and hilum lymph nodes. Later films showed a strong tendency to calcification of these nodes. The Pirquet test was positive.

At the time of her last admission to the Morrisania City Hospital, the patient stated that one month previously she developed large swellings behind the ears. Both masses felt hard and tender. She also stated that she had been having a low-grade fever. Examination revealed bilateral parotitis, a left

corneal scar directly in front of the pupil and old maculae around the periphery of the right cornea. Serial films of the chest were highly interesting since they could be compared over a period of two years before and after the appearance of lung changes. The films taken in January and December, 1936 showed no significant abnormalities. Films taken in November, 1937 revealed distinct enlargement of the hilum lymph nodes and stippled infiltrations extending into the adjacent parenchyma of the lung. Later films revealed an increase in the pulmonary involvement. A recent film (figure 10) shows these infiltrations to have progressed further into the midparts of both lungs. There were no bone changes. A Mantoux test, in the dilution of 1:1000, was negative. The patient is being followed in the clinic of the Morrisania City Hospital.

The films of our three patients presenting the uveoparotid syndrome revealed lung changes frequently observed in instances of noncaseating tuberculosis (5, 13). The hilum nodes are enlarged and radiating into the adjacent parenchyma of the lung there is often visible an interstitial stippling, described as having a marbled or reticulated appearance. The striations on the film are more prominent in the lower lobes and resemble lymphangitic carcinoma rather than miliary tuberculosis (figure 11). It is very likely that in these instances the lung markings are likewise due to a lymphangitic tuberculous process. A fine example of lymphangitic spread in tuberculosis, confirmed at necropsy, is reported by Hoyle and Vaizey (7). The patient described by these authors died in congestive heart failure caused by increasing obstruction of the pulmonary circulation. The histological features indicated that the condition had most likely arisen by direct lymphogenous extension from the hilum and was not haematogenous in origin.

Lymphogenous extension of tuberculosis, according to Stefko (20), may arise from subpleural tubercle or by direct permeation of the pulmonary lymphatics from the hilum lymph nodes. Although most physicians do not subscribe to retrograde lymphatic spread of tuberculosis, one cannot ignore such a possibility particularly when there is lymph stasis. The patient previously cited had originally normal hilum and lung markings. Later, it was noted that the lymph nodes were becoming enlarged and still later lymphangitic radiations were seen extending into the lung in a centrifugal manner. The evolution of the process was very suggestive of retrograde lymphatic permeation such as one sees in certain forms of malignancy involving the hilum lymph nodes.

3B. *Recurring, round infiltrates:* Following the contributions of Jaksch-Wartenhorst (10) and Albert (1), a number of reports describing round, tuberculous infiltrates in the lung appeared in the literature. These foci consist of circumscribed areas of caseation, well encapsulated, surrounded by healthy parenchyma. There is little or no glandular enlargement. The infiltrates have been found to retain their configuration for a long time. Occasionally, they excavate, ulcerate into bronchi and the disease extends in this manner. Rarely, as in an instance reported by Léon-Kindberg and Dugas (12), do they disappear completely. As far as can be learned from the reports on record, these round infiltrates are discovered on the film accidentally, their number as a rule remaining unchanged although the individual nodules may vary in size. The unusual feature in the case to be described was the successive appearance of new, round foci in a lung previously clear of disease. The significance of the joint manifestations is a matter of speculation. Attention has been directed to the occurrence of infectious polyarthritis in association with ocular tuberculosis (22).

Case 13: A. M., 38, admitted to the Montefiore Hospital August 9, 1926; died September 11, 1938. The patient's illness began in 1921 with pain and swelling of the ankles, knees and left shoulder. This was followed by partial stiffness of the joints. Five years later, in 1926, she was admitted to the Montefiore Hospital where a condition of polyarthritis was found. There were no symptoms referable to the chest. A routine film, in July, 1929, revealed no significant changes in the lungs. In the meanwhile she was treated for her arthritic condition with various physical measures.

In April, 1930, she complained of having developed a cough in the preceding few months. Although râles were audible over the right side of the chest, a film showed no abnormalities. In July, 1930, the right elbow-joint was resected. In December, 1930, an abdominal seizure necessitated the removal of an acutely inflamed appendix which was not tuberculous.

In February, 1932, she complained of impaired vision of her right eye. Examination revealed a uveitis. After careful study of the eye condition, the suggestion was made by Dr. B. S. Kramer that the patient had tuberculosis of the right eye. The diagnosis was based on the finding of lardaceous deposits in the anterior chamber of the eye. This was the first time tuberculosis was suspected, the patient having been throughout these years on the surgical service and in the Schiff (custodial) pavilion of the hospital. Shortly thereafter, in December, 1932, the patient complained of cough and chest pains. A friction rub was heard over the right chest. A film taken in August, 1933 revealed a large, round infiltration in the right lower lobe which had undergone cavity formation.

Following various forms of treatment, including tuberculin, the right eye was enucleated in April, 1936. Histological examination revealed a tuberculous iridocyclitis, retinitis and interstitial keratitis. In the meantime, the cavity in the right lower lobe was treated for a short time with pneumothorax and diaphragmatic paralysis, the latter supplemented with pneumoperitoneum. In July, 1935 a number of attempts were made to occlude the right lower bronchus leading to the cavity by means of instillation of a 25 per cent solution of acriflavine. For a time there seemed to be a diminution in the size of the cavity but in August, 1936 a new round infiltration appeared in the right upper lobe and another in the left upper lobe which rapidly underwent cavitation. Later, a similar infiltration appeared in the left lower lobe (figure 12).

FIG. 13

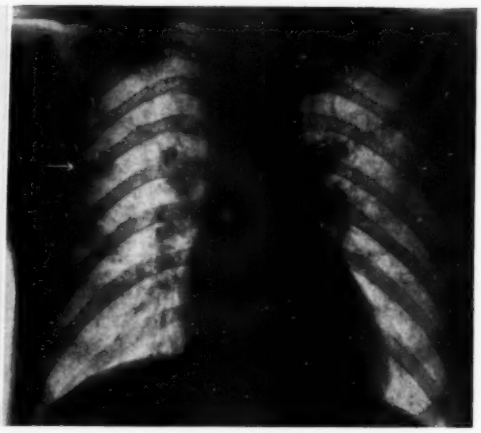

FIG. 14

FIG. 13. A. M. Necropsy, September 11, 1938. Specimen of left lower lobe of lung, showing circumscribed nature of lesion.

FIG. 14. H. A. December 31, 1926. Recent exudative infiltration in right upper lobe in course of urogenital tuberculosis. Calcific infiltrations in both upper lobes.

In the late months of 1934 and early 1935, sputum examinations revealed acid-fast organisms. During her later years repeated examinations of the sputum by concentration and guinea pig inoculations failed to reveal tubercle bacilli. Throughout this time, the patient had a low-grade fever, expectorated moderately and once had a copious haemoptysis. The skin reacted to 0.005 mg. of PPD. In the summer of 1938 the patient began to complain of headache. There was soon noted hypertension and an increase in urea nitrogen in the blood. She developed oedema of the ankles, other evidences of renal insufficiency and died in uraemia, September 11, 1938.

Postmortem examination, performed by Dr. L. Odessky, revealed in each lung several discrete cavities. These cavities, averaging 4 cm. in size, contained caseous material well circumscribed in fibrotic capsules. The surrounding lung parenchyma was free of disease (figure 13). The renal insufficiency and uraemia were apparently the result of contracted kidneys secondary to amyloid deposition in these and other visceral organs. Histological examination of the lung revealed areas of necrosis surrounded by zones of very cellular fibrous layers containing numerous epithelioid cells, lymphocytes and occasional giant cells. No acid-fast organisms were found.

C. Circumscribed Lung Lesions in the Course of Generalized Haematogenous Tuberculosis

The lungs and related structures serve both as a reservoir and as a filter of tubercle bacilli circulating in the blood-stream. Placed in this position, they are able to register on the roentgen film evidences of tuberculous infection affecting not only the pulmonary parenchyma but less easily visualized organs of the body as well. The appearance of the lung in instances of generalized haematogenous tuberculosis has been discussed in previous pages. There is bilateral seeding of tubercles of varying age, configuration, distribution and evolution. The picture presented in each instance depends on the character of the disease, in which a major and indefinable element is the nature of the symbiotic relationship existing between the host and the parasite.

In patients with chronic haematogenous tuberculosis, it happens occasionally that some organs escape with a minimum of infection or are able to overcome the infection while others are extensively involved. This applies also to the lungs. The apical parts of one or both lungs may reveal a number of tuberculous foci, fibrotic or calcific or both, which represent the remains of an antecedent, haematogenous seeding, yet, in the same individual, there may be present wide-spread tuberculosis elsewhere pursuing a protracted course with repeated haematogenous superinfections. This phenomenon is frequently observed in so-called "surgical" forms of tuberculosis, a condition characterized by minimal or arrested tuberculous changes in the lungs and ulcerative tuberculosis in the urogenital, osseous or other organs. There is no need to cite examples.

Because of the seeming dissociation of the disease in instances of "surgical" tuberculosis, it was the impression for many years that a certain antagonism existed between pulmonary and extrapulmonary tu-

berculosis. But in view of what is now known of the cyclical course of the disease, it is obvious that there can be no mutual exclusiveness of tuberculosis in different organs. Reisner (18) could find no such characteristic. His studies did confirm the fact that when tuberculosis involves an organ to the extent that it becomes the major seat of the disease, distant involvements are less likely to occur. This is in keeping with Ranke's concept of the evolution of tuberculosis: organic phthisis, the culmination of the disease, tends to be limited to one or a related group of organs.

Occasionally, as illustrated by the following instance, one encounters an isolated, exudative infiltration in the subapex of a lung in the course of chronic haematogenous tuberculosis.

Case 14: H. A., aged 22, admitted to the Montefiore Hospital August 3, 1925; left April 13, 1927. In February, 1921, at the age of 18, the patient entered the Montefiore Country Sanatorium. His history dated three months with the onset of cough, expectoration, fever and night sweats. Examination revealed tuberculous infiltrations in both upper lobes. The sputum contained tubercle bacilli on several occasions. He remained in the Sanatorium for 18 months, gained 17 lbs. in weight and the films, on discharge, revealed arrested disease. He returned to work.

Three years later he was admitted to the Montefiore Hospital with signs of urogenital tuberculosis, the symptoms of which had appeared about six months previously. Tubercle bacilli were found in the urine. A film of the chest revealed a calcified nodule in the extreme right apex and a few calcified tubercles in the left subapical region. Calcifications were noted in the cervical lymph nodes. Repeated examinations of the sputum failed to reveal tubercle bacilli. Subsequent chest examinations showed no change in the lung findings, the disease being confined to the kidney, bladder and epididymes. In December, 1926 a film of the chest revealed an exudative infiltration in the midportion of the right upper lobe (figure 14). The infiltration was not present on previous films, the last preceding one having been taken in May, 1926. There were no symptoms referable to the chest. The patient left the hospital in April, 1927.

Infiltrations of the nature described in the foregoing patient are of considerable interest from the point of view of the pathogenesis of pulmonary tuberculosis. The appearance of an isolated, subapical infiltration under circumstances where the probable source of infection is not as readily demonstrable as if the nidus were in a caseous lymph node for

example, would immediately raise the question whether one was dealing with endogenous or exogenous tuberculosis. If the individual happened to be a nurse or medical student in contact with tuberculous patients, the confusion would be all the greater. It bears repetition: haematogenous tuberculosis may give rise to a localized as well as a generalized disease. The significance of the circulatory channels in the evolution of pulmonary tuberculosis will be discussed in greater detail on another occasion.

REFERENCES

(1) ALBERT, A.: Mehrfache tuberkulöse Rundinfiltrate, Beitr. z. Klin. d. Tuberk., 1931, *78*, 647.

(2) BOECK, C.: Multiple benign sarkoid of the skin, J. Cutan. & Genito-Urinary Dis., 1899, *17*, 543.

(3) DUGGE, M.: Über einen Fall von "Sepsis tuberculosa gravissima" Geflügeltuberkulose?), Beitr. z. Klin. d. Tuberk., 1929, *71*, 538.

(4) GRETHMANN, W.: Protracted hematogenous multiform tuberculosis, Tr. Natl. Tuberc. A., 1936, p. 80.

(5) HANTSCHMANN, L.: Über torpide Formen disseminierter Tuberkulose, Beitr. z. Klin. d. Tuberk., 1930, *73*, 688.

(6) HEERFORDT, C. F.: Über eine "Febris uveo-parotidea subchronica," an der Glandula parotis und der Uvea des Auges lokalisiert und häufig mit Paresen cerebrospinaler Nerven kompliziert, Arch. f. Ophth., 1909, *70*, 254.

(7) HOYLE, C., AND VAIZEY, M.: Chronic miliary tuberculosis, Oxford Med. Pub., London, 1937.

(8) HUEBSCHMANN, P.: Pathologische Anatomie der Tuberkulose, Julius Springer, Berlin, 1928.

(9) HULL, T. G., AND HENKES, K.: The Widal test in tuberculosis, Am. Rev. Tuberc., 1923, *8*, 266.

(10) JAKSCH-WARTENHORST, R.: Pseudozystizerkosis vorgetäuscht durch Lungentuberkulose, Fortschr. a. d. Geb. d. Röntgenstrahlen, 1929, *39*, 1116.

(11) JÜNGLING, O.: Ostitis tuberculosa multiplex cystica (eine eigenartige Form der Knochentuberkulose), Ibid., 1919–1921, *27*, 375.

(12) LÉON-KINDBERG, M., AND DUGAS, J.: Tuberculose pulmonaire à forme de noyaux néoplasiques secondaires, Rev. de la tuberc., 1936, *2*, 457.

(13) LONGCOPE, W. T., AND PIERSON, J. W.: Boeck's sarcoid (sarcoidosis), Bull. Johns Hopkins Hosp., 1937, *60*, 223.

(14) MAYRHOFER, H.: Die rudimentäre Polyserositis und ihre Folgezustände, Beitr. z. Klin. d. Tuberk., 1934, *85*, 385.

(15) MILLER, W. S.: The relation of the pulmonary artery to the place of development of tubercles in the human lung, Tr. Natl. Tuberc. A., 1930, p. 219.

(16) PAGEL, W.: Pathologische Anatomie der hämotogenen Streuungstuberkulose, Ergebn. d. ges. Tuberk.-Forsch., 1933, *5*, 231.

(17) PINNER, M.: Noncaseating tuberculosis, Am. Rev. Tuberc., 1938, *37*, 690.

(18) REISNER, D.: The relations between extrapulmonary and pulmonary tuberculosis, Ibid., 1934, *30*, 375.

(19) SCHAUMANN, J.: Lymphogranulomatosis benigna in the light of prolonged clinical observations and autopsy findings, Brit. J. Dermat., 1936, *48*, 399.

(20) STEFKO, W. H.: Die pathologische Anatomie der lymphogenen Stadien der Lungentuberkulose, Ztschr. f. Tuberk., 1936, *76*, 113.

(21) SULZBERGER, M. B.: Sarcoid of Boeck (benign miliary lupoid) and tuberculin anergy, Am. Rev. Tuberc., 1933, *28*, 734.

(22) URBANEK, J.: Die Augentuberkulose in ihren Beziehungen zur Lungen- und Allgemeintuberkulose, Ergebn. d. ges. Tuberk.-Forsch., 1935, *7*, 148.

(23) WILSON, G. S.: Tuberculous bacillaemia, Med. Res. Council, Special Report Series, No. 182, London, 1933.

LIFE EXPECTANCY IN TUBERCULOSIS[1,2,3]

As Revealed by Case Fatality Rates

EMIL BOGEN

Experienced tuberculosis workers find it difficult to believe that the remarkable reduction in tuberculosis which has taken place during recent years has been due entirely to the prophylactic effect of isolation. The clinician, comparing the course of disease in patients with tuberculosis seen in the past with that observed under modern therapeutic measures, feels compelled to attribute at least a portion of the decline to the lower fatality rate among those infected. The failure of statistical investigations to reveal such effect is regarded by tuberculosis physicians as evidence of inadequacy of the statistical data or methods, rather than disproof of the value of sanatorium treatment and collapse measures (1). Reëxamination of previous studies, and a comparative analysis of available published data, as well as further study of the fate of a large number of patients followed for many years, accordingly appear desirable.

If it were true that the chances for recovery of patients with tuberculosis were not really increased by collapse therapy and other modern measures, but the patients merely made more comfortable, perhaps less heavily laden with tubercle bacilli, thus lessening the possibility for the wider spread of the disease, it might still be possible to argue for the extended application of these measures; but they would play a much smaller rôle in the campaign against tuberculosis than has recently been claimed for them. If, on the other hand, it can be proved that the average fatality rate of these patients is substantially decreased, this must represent a much greater increase in the life expectancy of those in whom the treatment is successful. The prolongation of a life of invalidism has been bemoaned, but there is no evidence to suggest that the actual capacity for work and play of those whose deaths are postponed by modern treatment is any lower than that of those treated successfully by earlier methods.

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[2] From the Olive View Sanatorium, Olive View, California.

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Although much may be learned regarding the relative efficiency of the various types of treatment of tuberculosis from a study of clinical reports, the changes in signs and symptoms and in laboratory findings during the course of treatment and immediately thereafter, the crucial test is undoubtedly the effect of the treatment on the life expectancy of the patients treated. Unfortunately, adequate information for the determination of the true life expectancy is generally lacking. Many attempts have been made on the basis of such information as is available to find some indication of what these figures would be.

The extensive statistical information available as a result of a general notification of tuberculosis makes possible an attack on this problem. If all of the patients reported diagnosed tuberculous for the first time, in any year, could be followed for a definite period of time and the number of deaths among them reported, the fatality rate per year in this group would be a measure of the effect of tuberculosis on their life expectancy, and could be compared with similar data for similar groups at other times and at other places. Unfortunately, adequate follow-up of known cases such as might be done by a central tuberculosis registry in this manner is still to be reported (2).

An attempt has recently been made to measure the effect of treatment in tuberculosis by comparison of the ratio of new cases reported annually to the number of deaths from tuberculosis occurring within the same year at different places and times (3). It has been recognized that differences in methods of reporting cases probably account for the greatest part of the differences in the case death ratios as reported in different places; but it has been boldly assumed that, in general, at any one place, the same methods have been followed and the figures for successive years are, therefore, comparable. From the fact that such ratios have shown little change in the past twenty years, the conclusion was drawn that there has been no substantial improvement in the efficiency of therapeutic measures in coping with tuberculosis (table 1).

The fact is, however, that the ratio of reported new cases to deaths from tuberculosis in any year is not a measure of the life expectancy for the patients so reported, and bears no necessary relationship to the efficacy of their treatment. Closer analysis of the figures available indicates that the true case fatality rate in tuberculosis has greatly diminished, although the ratio of deaths to new cases reported annually in many places appears to have remained constant. The importance of this matter in the further prosecution of the most important public

health campaign in the history of mankind justifies further examination of the data.

Patients do not ordinarily die of tuberculosis within the same calendar year in which they have become infected or even have developed first symptoms. The patients dying in sanatoria and public hospitals generally have been under treatment for about two years before death, and this figure has not changed much in more than a century (4). These deaths occurring within institutions, however, are for the most part instances of failure of treatment, or failure to use adequate treatment, and represent only a small proportion of the entire number of deaths eventually resulting from tuberculosis. Repeated studies have shown that most patients with advanced tuberculosis eventually die of this

TABLE 1

*Tuberculosis cases, deaths and case fatality in 1915 and in 1935 compared**

	NEW CASES REPORTED		NUMBER OF DEATHS		RATIO CASE FATALITY		PER CENT CHANGE
	1915	1935	1915	1935	1915	1935	
					per cent	*per cent*	
New York City	22,141	8,796	8,825	3,968	40	45	5+
Chicago	12,709	5,834	4,204	1,946	33	33	0
Detroit	1,517	2,062	650	787	43	38	5−
Philadelphia	6,289	2,236	3,088	1,238	49	55	6+
Upstate New York	9,950	5,765	5,404	2,839	54	49	5−
New Jersey	8,490	4,296	4,371	2,143	51	50	1−
Massachusetts	8,046	3,594	4,194	1,814	52	50	2−
England & Wales	68,309	39,635	40,803	24,603	60	62	2+

* Refer to Drolet (3).

disease, at least according to the death certificate. Many now are so reported decades after the original diagnosis. This long interval between the date of diagnosis and the date of death, well shown in the published table, contains an explanation for the erroneous conclusions which have been drawn (table 2).

Deaths from tuberculosis occurring within a community or institution in any one year should not be compared with the number of new cases reported admitted or discharged during that same year, as the latter may consist of an entirely different group of individuals. Comparison of the number of deaths from tuberculosis in various places with the number of new cases reported several years before the date of such deaths would give a more representative figure. Such calculation in-

dicates that a marked decline in the case fatality rates has actually occurred both in this country and in England during the past 20 years (table 3).

The figures for Chicago are omitted from these calculations since the

TABLE 2

*Tuberculosis—age of cases at time of reporting and at death, two-year period 1933–34, etc.**

	AVERAGE AGE OF NEW CASES REGISTERED		AVERAGE AGE OF ALL DYING FROM TUBERCULOSIS		DIFFERENCE BETWEEN AGE OF CASES AND OF THOSE WHO DIED	
	Male	Female	Male	Female	Male	Female
New York City	39.1	31.0	42.0	33.4	2.9	2.4
Chicago	36.4	28.1	40.4	31.3	4.0	3.2
London	35.2	29.5	41.4	33.6	6.2	4.1
Upstate New York	38.6	31.5	44.3	38.4	5.7	6.9
New Jersey	38.1	30.7	43.3	35.7	5.2	5.0
United States			41.5	35.8		
England & Wales	31.2	27.5	37.8	32.1	6.1	4.6

* Refer to Drolet (3).

TABLE 3

*Case fatality ratios in tuberculosis with a two year lag**

	NEW CASES REPORTED		NUMBER OF DEATHS		CASE FATALITY RATIO		CHANGE	PER CENT DECREASE
	1915	1933	1917	1935	1915–1917	1933–1935		
New York City	22,141	9,991	8,825	3,968	40.	40.	−0.2	−0.0
Detroit	1,517	3,351	790	787	55.	24.	−31.0	−56.0
Philadelphia	6,289	2,538	3,381	1,238	54.	49.	−5.0	−0.9
Upstate New York	9,950	6,297	5,675	2,839	57.	45.	−12.0	−20.0
New Jersey	8,490	4,461	4,617	2,143	54.	48.	−6.0	−12.0
Massachusetts	8,046	3,541	4,559	1,814	57.	51.	−6.0	−10.0
England & Wales	68,309	49,958	42,335	24,603	62.	49.	−13.0	−20.0

* Refer to Drolet (3).

notifications there recorded for 1915–1920 are swollen by duplicates and reports on cases actually diagnosed years before (5).

The difference between the average age at the time of notification of the diagnosis of tuberculosis, and the average age at death from this disease may be taken as the average duration of the disease following such notification. This difference, in the places for which such data are available, has increased by several years in the past decade (table 4).

In view of the increasing age at the time of notification, it is probable that if the actual differences between the time of notification and of death in the individual cases were taken, instead of the averages in the same year, an even greater prolongation of life might be revealed. At any rate, the figures appear to show conclusively that the average duration of the disease has been rapidly increasing even in the patients who do die of it, and the differences are certainly great enough to cause a marked drop in the true "fatality rates" if these could be correctly determined.

TABLE 4

*The changing average duration of tuberculosis, 1925 and 1935**

	MALE			FEMALE		
	Average age registered new cases	Average age tuberculosis deaths	Difference	Average age new cases	Average age tuberculosis deaths	Difference
New York Upstate						
1925	34.5	38.7	4.2	30.2	34.1	3.9
1935	39.0	44.4	5.4	32.3	38.6	6.3
Increase	4.5	5.7	1.2	2.1	4.5	2.4
New Jersey						
1924	34.8	38.5	3.7	30.1	31.6	1.5
1934	36.7	42.3	5.6	30.8	36.2	5.4
Increase	1.9	3.8	1.9	0.7	4.6	3.9
England & Wales						
1924	27.9	32.6	4.7	25.0	29.0	4.0
1934	31.2	38.6	7.7	27.0	32.8	5.8
Increase	3.3	6.3	3.0	2.0	3.8	1.8

* Refer to Drolet (3).

The increase in the duration of disease as shown by the above figures suggests, in fact, that a better approximation of the true fatality rate might be obtained by assuming that there was a lag of about two years between notification and death in 1915, about four years in 1925 and about six years in 1935. If we take the ratio of deaths in 1917 to cases reported two years earlier, and the ratio of deaths in 1935 to cases reported six years earlier, accordingly, a much greater drop in the real case fatality rates is indicated (table 5).

The decrease in the average annual case fatality ratio, disclosed by taking into consideration the delay between the notification of diagnosis and of death, agrees with that suggested by the increased age at death

and by the prolonged survival time in the available data, as well as with general clinical experience. This finding is just as definite and important as the decrease in the general mortality rates from tuberculosis, and indicates that a large part of the decline in the death rate from this disease is due to a drop in the fatality rate among those afflicted. There is no doubt but that the decrease in the general incidence of infection resulting from institutionalization and isolation is an important factor in the decline in the incidence and mortality of the disease, but the data reviewed do not justify the implication that it is the only factor concerned.

The drop in the case fatality ratio and the increased duration of the disease in the fatal cases need not be attributed entirely to the effects

TABLE 5

*Case fatality ratios in tuberculosis with a two year lag in 1915 and a six year lag in 1935**

	NEW CASES REPORTED		DEATHS REPORTED		CASE FATALITY RATIO		PER CENT CHANGE	
	1915	1929	1917	1935	1915–1917	1929–1935		
New York City	22,141	11,938	8,825	3,968	40.0	33.0	7.0	−17.0
Detroit	1,517	3,006	790	787	54.0	26.0	−28.0	−52.0
Philadelphia	6,289	2,724	3,381	1,238	54.0	45.0	−9.0	−16.0
Upstate New York	9,950	7,487	5,675	2,839	57.0	38.0	−19.0	−33.0
New Jersey	8,490	5,223	4,617	2,143	55.0	41.0	−14.0	−26.0
Massachusetts	8,046	4,538	4,559	1,814	57.0	40.0	−17.0	−30.0
England & Wales	68,309	57,274	42,335	24,603	62.0	43.0	−19.0	−31.0

* Refer to Drolet (3).

of modern improved treatment. The diminished opportunities for reinfection after leaving the sanatorium, the better after-care now generally available, and the lowering of industrial pressure due to the depression may have given patients a better chance in recent years. Crude case fatality ratios, and duration of disease since notification, may be highly misleading, since notification is confessedly inadequate and dependent upon many changing local factors, and the condition of the patients at the time of notification varies widely. To the extent that such figures may be used, however, the above analysis shows that they are completely consistent with the general observation that active treatment in tuberculosis is a life-saving measure and gives no support to therapeutic nihilism in this disease.

The fact that the majority of patients dying of tuberculosis have not

had the advantage of modern treatment leads us to expect an even greater improvement in the records of treated cases, if such data were available (6). Numerous studies have been made of the results obtained and the percentage of patients dying while under treatment in sanatoria. Differences in the condition of the patients at the time of admission to the various sanatoria, their length of stay in the institution, and the criteria for discharge account for many of the discrepancies observed. The recent emphasis on the value of isolation causes many institutions now to keep terminal patients who would formerly have been sent home to die.

The general impression that the excess death rate from tuberculosis practically disappears within a few years of admission or discharge, is based mainly on failure to compute properly the true number of patient years' exposure, and on the admission of literally terminal cases. Examination of the data fails to confirm this impression, but suggests instead that the risk of death from tuberculosis is a perpetual sword of Damocles hanging over the survivor, and that the death rate among the remaining patients in the same stage of the disease shows little change from year to year. Examination of a large number of follow-up studies in patients with tuberculosis indicates that the death rates in patients of the same stage following discharge from the sanatoria, or preferably from the time of admission until death or last report, shows a remarkable uniformity.

"The end results of sanatorium care, quite irrespective of the location of the institutions, are strikingly similar. Incipient cases give the best promise, although the sanatoria cannot quite wipe out the effects of the disease in even such cases. The records of the best sanatoria of the country show clearly that the after-mortality among the graduates is from two to three times the normal for age. Those who have been admitted in a moderately advanced stage of the disease have a subsequent mortality from eight to ten times the normal for age, and those who have been admitted as far advanced cases show a mortality from thirty to forty times the normal for age" (7).

Expressing results in terms of the percentage increase in mortality rates over the expected figures is apt to be misleading, since the denominator changes greatly so that a condition killing 10 per cent at all ages will kill twenty times the normal at age 25, but only two times the normal at age 60. Sex and other factors affecting the general expected death rates also disturb this ratio. Accordingly, any group having

a low naturally expected death rate, such as children, women, etc., will appear to have a much higher ratio of tuberculous deaths to expected deaths than do those with a higher natural expectation. This is apt to be just the reverse of the actual relations. The difference between these rates, rather than the quotient, would give a much better picture of the frequency of deaths due to tuberculosis. Moreover the death rate in tuberculous patients is so much higher than general expectation that the latter may generally be neglected entirely for practical purposes.

The total number of deaths reported, divided by the number of patient years of observation, gives the average annual fatality rate. The tremendous difference in life expectancy in the different stages of tuberculosis, however, makes it necessary to consider each stage separately, or to make some correction for variations in the distribution of such cases. When the annual fatality rate of patients in each of the three stages of the disease is known, the fatality rate in a group of patients consisting of equal numbers of each of the three stages may be calculated by dividing the sum of these rates by three.

This standard unit, the combined average annual fatality rate, makes possible a convenient comparison of the results obtained in different groups of patients. It may be used for the study of prognostic factors as well as for the evaluation of therapeutic measures in patients with tuberculosis. Comparison of the results published from different places, where the criteria for admission and discharge and the adequacy of the follow-up information varies so greatly, presents considerable difficulty and many sources of error. Nevertheless, it is interesting to observe that in a large series of follow-up studies of patients following discharge from different sanatoria, although the crude death rates in these groups varied tremendously, the combined average annual rate above described for these patients was generally not far from the average of 11 per cent per year.

In a single institution, where the policies and definitions are more stable, it may be possible to compare the results with greater assurance. For this reason, the records of all of the admissions to the Olive View Sanatorium from 1920 to 1937 have been analyzed. All charts were reviewed and more than 10,000 X-ray films were reread in the effort to classify all cases on a uniform standard. The follow-up information on these patients is exceptionally complete, only 10 per cent having been lost sight of more than a year before the making of this study. The actual number of days that each individual patient had been

followed from the date of first admission to the date of death or the date last heard from was determined. The rates were then calculated in terms of the number of deaths per patient year of observation.

Patients admitted to the Olive View Sanatorium during the latter half of this period have shown a definitely lower fatality rate during the entire time of observation than have those who were admitted in the earlier years. Even more marked is the lowering of the fatality rate among all patients observed during the last eight calendar years, irrespective of the date of admission, as compared to the figures observed before the depression. This may be ascribed to the fact that the sur-

TABLE 6

Fatality rates in 7,789 patients with pulmonary tuberculosis at the Olive View Sanatorium, 1920–1937

	PATIENTS	AVERAGE ANNUAL FATALITY RATE			
		Minimal	Moderately advanced	Far advanced	Combine
Total	7,789	1.3	4.6	21.6	9.3
Admitted in					
1920–1928	3,153	1.4	5.9	26.0	11.1
1929–1937	4,636	1.1	2.4	18.0	7.2
Observed during					
1920–1928	3,153	1.3	7.0	38.0	15.4
1929–1937	5,279	1.3	2.5	17.0	6.9
Observed during					
0–8 years after admission	7,789	1.2	4.6	23.0	9.6
9–16 years after admission	665	1.6	2.7	11.0	5.1

vivors of the earlier years may now avail themselves of any advances in treatment open to the new admissions, as is indicated by the large number of readmissions among these patients. Accordingly, the fatality rates are lower for patients after the first eight years following admission, despite the aging of the average survivor at this time.

Closer examination of the figures shows that the drop in the average annual fatality rates is due mainly to the improvement among the advanced cases, for whom modern collapse therapy measures are suitable, and that very little difference may be observed among the minimal cases, whose treatment to-day is little different from that of decades

past. Cavity cases have a fatality rate many times that of noncavity cases, positive-sputum cases have a death rate many times that of negative cases, and the death rate increases with increasing numbers of organisms in the sputum. The percentage of patients admitted to Olive View with far advanced disease, cavity and positive sputum has varied very little in these seventeen years. The annual fatality rate among patients having positive sputum at the time of discharge has also shown little change. The marked drop in the annual fatality rates, accordingly, is mainly attributable to the greater number of cavity closures and sputum conversions produced in the institution in more recent years. Further studies are in progress to show the extent to which various collapse therapy measures may be credited with the unmistakable decline in the tuberculosis case fatality rate among our patients.

REFERENCES

(1) BRIEGER, E.: After-care and rehabilitation, Brit. J. Tuberc., Supplement, October, 1937, vol. *31*.

(2) MOORE, F.: A study of 2739 cases of tuberculosis reported to the San Francisco Department of Public Health, W.P.A. Project #3724, October, 1937.

(3) DROLET, G. J.: Present trend of case fatality rates in tuberculosis, Am. Rev. Tuberc., 1938, *37*, 125.

(4) ELDERTON, W. P., AND PERRY, S. J.: A third study of the statistics of pulmonary tuberculosis, Drapers' Company Research Memoirs VI, 1910.

(5) Biennial Report, Bulletin of the Chicago Municipal Tuberculosis Sanitarium, 1923–24, July–August, 1925, *5*, 24.

(6) ROSENBLATT, M. B.: Collapse therapy in pulmonary tuberculosis, Correspondence, J. A. M. A., 1938, *110*, 2170.

(7) DUBLIN, L. I.: Health and wealth, 1927.

CASE FATALITY RATES IN TUBERCULOSIS

A Second Note with Reference to Methods of Comparing Reports of Cases and Deaths in Certain Communities

GODIAS J. DROLET[1]

One cannot but welcome any evidence that modern treatment of tuberculosis is more effective than formerly. The observation of Bogen (1) that Olive View Sanatorium patients admitted in more recent years show *so far* "a lower fatality rate . . . than those who were admitted in the earlier years" is an interesting contribution.

But with only incomplete work data given, one may wonder, first—though it is claimed that "the percentage of patients admitted to Olive View with far advanced disease . . . has varied very little in . . . seventeen years"—whether, in view of the increasing use of the X-ray during that period and the nation-wide development of "early diagnosis" campaigns, there was not instead lately a higher proportion of earlier and more favorable cases coming for treatment. Second, it is stated that in the follow-up "10 per cent" were "lost sight of more than a year before the making of this study," a number totalling nearly 800 and among whom many deaths may have occurred. Between these untraced cases and the shorter period of observation of patients more recently discharged it is obvious that the fatalities in the second group of patients are relatively incomplete.

It is this particular difficulty of ascertaining the ultimate results of treatment of tuberculosis cases in an institutional group that led me to undertake the study on the *Trend of Fatality Rates* (2) in entire communities, since practically all deaths from all causes are registered nowadays. Furthermore, in community records we deal with the entire group of the tuberculous population, not only those seen in country sanatoria but likewise those in city hospitals, or in clinics or in private medical practice.

Bogen has, however, made the valuable suggestion that when comparing community reported cases and recorded deaths the ratio should not be established simultaneously for the same year but rather that the

[1] New York Tuberculosis and Health Association, New York City.

number of deaths should be lagged some time after the cases. Still it should be remarked that, even if by computing ratios for the same year we have not an absolute complete case fatality rate, at least we do have, when the method is followed similarly at both the beginning and end of the period studied, as I did between 1915 and 1935, a comparable yardstick. And if it be true that the deaths noted in 1915 occurred among cases originally reported in previous years, it is likewise true that the same situation existed among those dying in 1935.

Before following the suggestion of lagging the deaths for a period of time after the cases have been reported, let us see first what has happened to the tuberculosis death rate in the communities reported upon. This will enable us to see whether the changes in case fatality rates under different modes of computation are commensurate with or in proportion to the trend in the general tuberculosis record.

Tuberculosis death rate in 1915 and in 1935*

PLACE	YEAR 1915	YEAR 1935	CHANGE 1935/1915
New York City	196	60	Decrease 136 = 69%
Philadelphia	185	61	Decrease 124 = 67%
Chicago	171	56	Decrease 115 = 67%
London	199	77	Decrease 122 = 61%
"Up-State" New York	132	52	Decrease 80 = 61%
New Jersey	154	50	Decrease 104 = 68%
Massachusetts	136	45	Decrease 91 = 67%
United States	146	55	Decrease 91 = 62%
England and Wales†	115	55	Decrease 60 = 52%

* Per 100,000 population.

† Standardized death rate from pulmonary tuberculosis.

As against this almost universal reduction in the tuberculosis death rate by two-thirds or more during those twenty years, let us now examine, as suggested by Bogen, the case fatality rate by lagging the deaths two years after the number of cases, comparing, for instance, the ratio of the deaths in 1917 to cases in 1915 and again the deaths in 1935 against the cases in 1933. First, the improvement of the case fatality, limited to some places, is nowhere near what has taken place in the general tuberculosis rate and, second, the change in the ratios thus obtained demands for its interpretation close knowledge of local conditions.

With regard to New York City, where so many activities have been developed against tuberculosis in recent years, this method of comparing

case fatality ratios reveals no change: 40 per cent formerly, 40 per cent lately; and yet here the tuberculosis death rate fell by 69 per cent. In Philadelphia, comparing ratios with a two-year lag, they do change from 54 to 49, namely, by five points or 9 per cent—though in the meanwhile the community tuberculosis death rate was coming down by 72 per cent. Chicago, Bogen would ignore. Personally, I am very familiar with that community and the unusual development there of a highly unified central control of tuberculosis under the Chicago Municipal Sanitarium. It is one place particularly where the record should be studied. The case fatality ratio of the 1917 deaths against the 1915 cases was 30 per cent; that of the deaths in 1935 against the cases in 1933 was higher, 35 per cent, an increase of five points or a 17 per cent rise. Still, accepting the statement that from 1915 to 1920 notifications were swelled by duplicates, the comparison may then be made at a later date, for instance, taking the deaths in 1925 (2,489) against the cases in 1923 (10,105) when we find a fatality rate of 25 per cent. But the ratio of the 1935 deaths (1,946) to the 1933 cases (5,485) was 35 per cent, showing no improvement and instead a rise of ten points or an apparent increase in the case fatality rate during those ten years of 40 per cent.

Detroit, by this method of lagging the data, would show a tremendous lowering of the case fatality ratio, from 55 down to 24, according to Bogen. The first figure is an error and should have been set at 52; furthermore, certain conditions in that community eliminate all this favorable evidence. It is unfair to compare the deaths in 1935 (787) against the cases in 1933 (3,351) since, as carefully pointed out by the Detroit authorities, at that time the register included a large number of "childhood type of cases"—a group of course not included in the registration of cases in 1915. The undue loading caused by this improper entry in a register of active cases of tuberculosis is very obvious when we see that in 1934, with the practice corrected, the reported cases numbered only 2,225—1,126, or 33 per cent fewer than just the year preceding. Second, in Detroit particularly, and as is happening increasingly in many other places because of the extreme growth of institutional facilities during the past twenty years and their location frequently outside the cities themselves, deaths now recorded locally are notoriously short of the complete mortality of their residents. For instance, in Detroit in the year 1935, besides the 787 deaths from pulmonary tuberculosis recorded locally, the Department of Health has informed me directly that 139 of their residents were known to have died out of town, especially

at the Maybury Sanatorium, Northville, or in state institutions and other places. Therefore, the locally recorded deaths were 18 per cent short of the reality. And, if we were to compare the total mortality of 1935 against only the adult type of cases reported in 1933, as was done for 1917 against 1915, most of the apparent gain in the case fatality ratio in Detroit would be wiped out.

The growth of institutional facilities colors practically all of the mortality records of certain cities in recent years to an extent far greater than formerly. In my annual survey of tuberculosis in large cities of the United States I have been directly informed by Health Commissioners of material numbers of their residents dying out of town. Minneapolis, for instance, in 1935 as against a recorded mortality locally of 72 had in addition 113 deaths of its residents outside the city, mostly at the Glen Lake Sanatorium; Milwaukee, besides 168 local deaths, had 163 out of town; Philadelphia had 105; Chicago, 234; New York City, 535. And it is probable that there are many other additional deaths in western resorts which are never brought back into the local records.

"Up-State" New York would seemingly have an improvement in its fatality ratio from 57 to 45, or 21 per cent. But here, too, recent changes interfere with the exact comparison of conditions now with those formerly. The Catskill and the Adirondack regions of "Up-State" New York were long sought by health seekers. The economic depression has, however, greatly curtailed the exodus of patients from the cities. Thus, for instance, the tuberculosis deaths recorded in 1917 in Essex, Franklin and Sullivan counties of the State of New York numbered 497, most of them among patients drawn from the large communities, especially New York City. But in 1935, in these same counties, the tuberculosis deaths numbered 278, a reduction in number of 43 per cent. It is well known nowadays that health resorts are comparatively deserted, but the effect upon the recorded death rate of "Up-State" New York is a favorable one due not to improvement necessarily of sanatorium treatment but in part to the mere fact that patients in New York City cannot afford, as formerly, to go there for treatment. If one took, therefore, into account for "Up-State" New York the reduced mortality from a lesser use of the health resorts in just these three counties, the percentage of improvement in the case fatality rate would be reduced to around 14 per cent, while the tuberculosis death rate "Up-State" was coming down by 61 per cent.

In New Jersey and in Massachusetts, the improvement in the fatality

ratio of 10 or 12 per cent must be set also against reductions in their tuberculosis death rate of 67 or 68 per cent.

In England and Wales, comparison by Bogen of the deaths in 1935 (24,603) against cases in 1933 (49,958) is not altogether warranted since in the latter instance there is included both so-called primary and supplemental returns whereas the 1915 cases were only those arising from primary notifications. From the 1933 cases should be removed 5,476 supplemental returns. The corrected case fatality ratio would then be 55 per cent instead of 49 and the improvement of seven points from 62 would represent a 12 per cent reduction—while the death rate was coming down by more than 52 per cent.

Avoiding in the United States difficulties in certain communities because of changes in local conditions, it is useful to utilize the available reports of the United States Public Health Service, which take in large areas. Thus, for instance, in 1924 in twenty of the more important states, which contained the majority of the population of the country, 98,623 cases were reported and in these same states, in 1926, 52,828 deaths or a case fatality rate of 54 per cent. Bringing the comparison up to as late a period as possible—for instance taking the deaths in 1937 (67,012) against the cases in 1935 (111,856), as reported by the National Tuberculosis Association this time for the entire country—with a two-year lagging, the ratio is not lower but instead actually higher, 61 per cent.

The further suggestion of Bogen that in a comparison of the deaths against the cases the lag formerly and now should be on different bases, namely, two years at the beginning of the period studied and six years at present, is manifestly unwarranted if we but give thought to the rapid decline of tuberculosis nowadays. For instance, in the six years alone preceding 1935 the tuberculosis death rate in the United States has come down by 27 per cent and the annual rates have been as follows:

Year	*Rate*	*Year*	*Rate*
1929	76	1933	60
1930	71	1934	57
1931	68	1935	55
1932	63		

It is obvious, therefore, that with such a rapid and continuous decline almost any improvement desired in the case fatality ratio could be obtained by starting at a date when conditions were fixed at a nearly

stationary level and selecting at the end of the period a lengthening lag for the comparison of deaths against cases. This method would be particularly advantageous if we recall that around 1915 for a while the tuberculosis death rate was not only stationary but at times even going up. In 1915, it was 146; in 1916, 142; in 1917, 147; and, in 1918, with the influenza pandemic raging, 150.

But, as has been well remarked, the normal evolution of pulmonary tuberculosis is not one readily changed and the assumption that the average duration of cases has been materially modified of late demands more precise confirmation than is available to date. On this score of the remaining seriousness of tuberculosis, let us but quote from the remarkable and recent observations of Zacks in a rather unusually well followed-up group of cases in Massachusetts. In a paper not yet published, Zacks refers to 320 families, consisting of 2,036 members and where there was a history of contact among children, stating that during the period of observation (averaging slightly more than four years) 791 cases of pulmonary tuberculosis were discovered of which 351 died—"a case fatality of 41 per cent in the males and of 45.5 in the females."

In conclusion, case fatality ratios, whether computed by comparing the deaths of a given year against the cases reported at the same time, or by lagging the number of deaths to two years later, continue to remain high; and, when lower, the improvement is nowhere commensurate with or proportionate to the extreme decline of the general tuberculosis death rate during the period studied.

REFERENCES

(1) Bogen, E.: Life expectancy in tuberculosis, Am. Rev. Tuberc., 1939, *39*, 587.
(2) Drolet, G. J.: Present trend of case fatality rates in tuberculosis, Ibid., 1938, *37*, 125.

TUBERCULOSIS MORTALITY IN INDUSTRIAL POPULATIONS OF MASSACHUSETTS AND MICHIGAN[1]

C. C. DAUER

In other studies on tuberculosis mortality marked differences have been demonstrated in different areas of this country (1). In some instances relatively high rates have been found in areas or states with relatively high percentages of industrial populations (2). This paper is a report of a study of tuberculosis mortality in two groups of cities which were approximately the same size according to the 1930 census, and in which a large proportion of the populations were engaged in industrial occupations. Four cities in Massachusetts were selected on this basis (Fall River, Lawrence, Lowell and New Bedford) and a like number in Michigan (Flint, Grand Rapids, Pontiac and Saginaw).

DESCRIPTION AND SOURCE OF DATA

The mortality data used in this study were tabulated by the author from the original or copies of death certificates filed with the state bureaus of vital statistics in Massachusetts and Michigan, and from the records of the Division of Tuberculosis in the Massachusetts State Department of Public Health. All other statistical data relating to the eight cities appearing in tables 3, 4 and 5 were taken from published reports of the Bureau of the Census.

The number of deaths from tuberculosis in the Massachusetts cities was tabulated for alternate quinquennial periods from 1875 to 1929. The number of deaths for the Michigan group was taken for only four quinquennial periods from 1900 to 1929 because previous to 1900 reliable mortality data by cities in Michigan are not available.

It was impossible to collect data for each five-year period for the Massachusetts cities from 1875 to 1929, and for the Michigan cities from 1900 to 1929, because of a limited amount of time available for assembling the material. The quinquennial period, 1925–1929, was made the terminal point of the study because reasonably accurate estimates of population could not be made for any period since 1930.

[1] This study was made possible by a grant from the National Tuberculosis Association.

There is ample evidence to indicate that marked changes in the population of some of these cities have occurred since 1930, which would make any calculation of rates by sex and age quite unreliable.

MORTALITY FROM TUBERCULOSIS IN THE TWO GROUPS OF CITIES

In tables 1 and 2 the mortality rates for each city are tabulated by sex for all ages and for certain broad age groups. Mortality rates by age groups for Flint and Pontiac had to be omitted for the quinquennial periods 1900–1904 and 1905–1909 because there are no estimates of population by age and sex for either the 1900 or the 1910 census.

Mortality for all ages: In three of the four Massachusetts cities tuberculosis mortality rates for males were at approximately the same high level in the 1875–1879 period, that is, between 366 and 376 per 100,000 population. In Fall River the rate was 268. In the quinquennium 1905–1909 the rates for males in these cities varied between 181 and 230 per 100,000 and in 1925–1929 from 77 to 130.

Among females in the Massachusetts cities mortality rates varied between 385 and 472 per 100,000 population in the 1875–1879 period, by 1905–1909 they had declined by more than 50 per cent and in the 1925–1929 period they varied between the limits of 63 and 101.

The principal point to be noted regarding the Massachusetts cities is the fact that female rates were considerably higher than those for males (by about 20 per cent) in 1875 but due to a more rapid decline in mortality they were approximately 20 per cent lower than those for males in 1929. The sex differences in trends of tuberculosis mortality in Massachusetts and Michigan have been reported in a previous paper (3) and consequently will not be discussed here.

In three of the four Michigan cities male rates were slightly over 100 per 100,000 population in the 1900–1904 period, and in the fourth city (Flint) it was only 63. In the 1925–1929 period male rates had declined slightly less than 50 per cent on the average as compared with the 1900–1904 rates.

There was more variation in female rates for the Michigan cities in the 1900–1904 period than for males. For the former they varied from 72.5 to 129.5. On the average the rates in 1925–1929 were slightly more than 50 per cent lower than in 1900–1904.

In the Michigan cities there was little difference in male and female mortality from tuberculosis from 1900 to 1929. The trend of mortality has also been essentially the same for males and females, about 47 per cent decline for males and 51 per cent for females.

It is quite evident, when the rates for the two groups of cities are compared, that wide differences have existed in the rates for the two

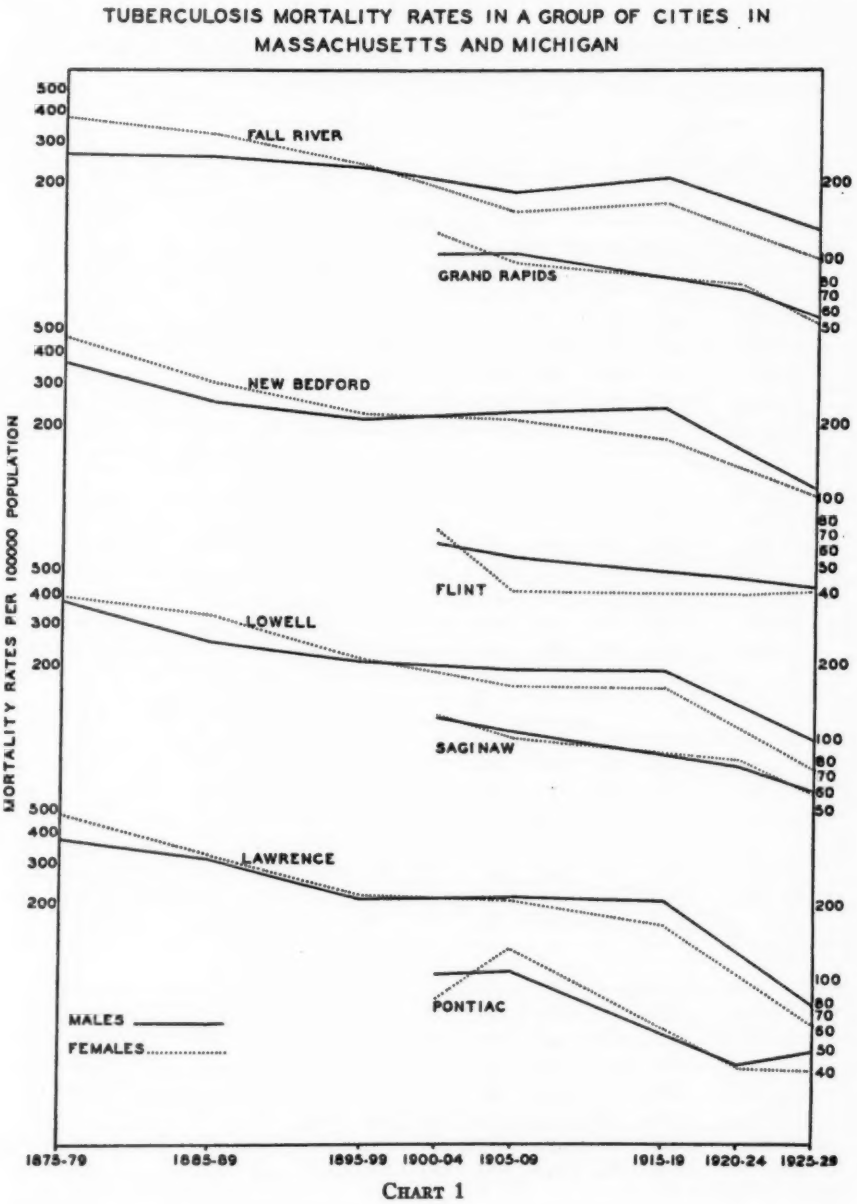

CHART 1

groups. (See chart 1.) Both male and female rates have been almost twice as high in the Massachusetts group as compared with the Michigan

group over the same period of time. The decline in mortality among males has been essentially the same in the two groups but on the average

TABLE 1

Tuberculosis mortality rates per 100,000 population by sex for all ages and by age groups in Fall River, Lawrence, Lowell and New Bedford, Massachusetts

	MALES						FEMALES					
	1875–79	1885–89	1895–99	1905–09	1915–19	1925–29	1875–79	1885–89	1895–99	1905–09	1915–19	1925–29
Fall River												
All ages	268	257	230	181	208	130	386	322	231	155	168	99
0–14	115	76	67	56	81	54	124	99	80	66	82	32
15–24	288	357	238	138	176	127	467	438	285	184	250	158
25–34	260	395	412	278	270	162	527	500	463	273	246	148
35–44	375	330	328	322	363	161	438	424	285	163	234	108
45–64	417	400	308	247	292	217	418	302	167	106	119	86
65+	520	368	333	240	223	133	762	404	165	87	94	114
Lawrence												
All ages	376	311	210	213	207	77	472	324	220	210	166	63
0–14	154	106	61	93	94	44	177	105	61	86	83	24
15–24	482	405	222	104	128	53	647	441	262	217	213	101
25–34	410	467	315	242	241	96	636	541	375	266	260	103
35–44	480	400	355	257	313	124	385	333	297	231	171	75
45–64	411	290	247	263	291	114	450	248	145	203	125	47
65+	650	487	177	300	170	111	694	282	264	83	80	35
Lowell												
All ages	366	250	210	190	190	99	385	324	218	166	163	74
0–14	128	122	78	88	111	38	151	154	100	87	117	24
15–24	373	230	253	120	157	61	463	393	277	177	187	115
25–34	381	322	301	242	211	97	484	498	311	264	214	120
35–44	423	330	283	267	282	147	409	401	254	211	195	107
45–64	510	387	254	213	213	186	290	220	185	120	131	54
65+	748	204	160	92	171	89	509	300	148	72	65	53
New Bedford												
All ages	365	243	210	230	237	110	466	300	221	210	178	101
0–14	176	145	122	107	112	54	206	207	154	133	139	70
15–24	332	251	219	165	226	95	600	367	314	210	180	172
25–34	350	322	348	266	241	154	444	422	347	322	215	134
35–44	327	270	178	211	287	181	478	333	158	181	177	106
45–64	466	303	290	240	289	113	270	193	186	128	97	71
65+	725	494	224	253	178	114	909	367	368	345	117	54

the decline among females has been slightly greater in the Massachusetts group.

Mortality rates by age groups: The principal reason for presenting these data is to demonstrate the fact that, among all age groups of each sex,

TABLE 2

Tuberculosis mortality rates per 100,000 population by sex for all ages and by age groups in Flint, Grand Rapids, Pontiac, and Saginaw, Michigan

	MALES				FEMALES			
	1900–04	1905–09	1920–24	1925–29	1900–04	1905–09	1920–24	1925–29
Flint								
All ages	63.0	56.4	45.4	41.7	72.5	40.5	38.7	40.0
0–14			23.4	17.7			22.2	14.9
15–24			40.3	29.4			42.6	70.1
25–34			38.4	40.0			55.6	36.0
35–44			63.6	54.0			50.2	42.7
45–64			61.7	84.4			35.0	42.0
65+			145.4	96.1			26.1	94.3
Grand Rapids								
All ages	105.2	107.1	75.3	56.5	129.5	96.0	78.5	52.5
0–14	45.7	41.1	19.3	10.3	45.1	45.9	29.0	17.7
15–24	195.2	154.3	92.3	54.5	233.3	121.4	111.2	87.1
25–34	167.3	156.9	76.4	76.6	208.7	136.7	125.7	74.1
35–44	128.6	123.3	112.0	114.0	93.3	107.2	78.8	45.6
45–64	98.6	96.1	92.1	70.2	88.0	90.1	56.3	46.7
65+	51.8	103.4	62.2	43.7	107.0	104.0	28.5	51.9
Pontiac								
All ages	104.5	109.0	43.7	49.1	81.8	136.1	43.1	40.3
0–14			23.0	29.6			23.5	13.7
15–24			31.8	41.2			47.0	59.5
25–34			59.0	55.0			31.6	60.4
35–44			38.4	68.8			68.4	44.0
45–64			64.3	49.4			53.1	30.8
65+			73.2	120.0			69.4	54.5
Saginaw								
All ages	112.0	106.7	77.6	60.4	113.1	100.0	80.9	58.5
0–14	28.4	12.2	25.1	25.9	12.5	30.8	26.0	23.1
15–24	155.7	152.5	73.8	69.2	197.6	187.6	141.0	106.7
25–34	192.6	147.3	106.6	72.8	236.8	137.0	127.2	112.9
35–44	120.0	156.2	123.4	76.4	116.1	96.1	101.1	46.1
45–64	111.4	125.2	94.6	89.5	59.0	86.3	55.0	33.1
65+	167.8	103.4	103.8	36.8	20.2	16.4	53.7	26.8

tuberculosis mortality has been higher in the Massachusetts cities than in the Michigan group. In the years for which data are available for

each group of cities this difference has been consistently maintained. When the rates by age groups for males in one group are compared with males of the other, the greatest difference noted is in the magnitude of the rates. The highest mortality in males is now found in the middle and older ages of the Michigan as well as the Massachusetts cities. Likewise, in both groups of cities the female curve of mortality is the same except that the rates are higher in each age group in the Massachusetts cities. Among females the highest rates are found in the young adults.

ENVIRONMENTAL AND SOCIAL CONDITIONS

The reason for the marked difference in tuberculosis mortality of the two groups of cities is not clear. There are certain suggestions to be found in the character of the two groups which will now be discussed. Similarities as well as differences in conditions prevailing in each group of cities will be pointed out. Any discussion of such environmental factors as geographical and climatic will be omitted because definite information is lacking.

Population: Although all of the cities were approximately the same size in 1930 their population showed quite marked differences in the half-century just preceding. The population of the Massachusetts group increased steadily from 1870 until 1910 (see table 3). During the next decade there was a slowing up in the growth of population in these cities and a decrease was recorded in the 1930 census. With the exception of Grand Rapids, the Michigan cities were small cities of less than 10,000 population in 1870. Grand Rapids had a steady growth from 1870 to 1930 and Saginaw from 1880 to 1930. Flint and Pontiac experienced very rapid increases in population from 1910 to 1930 coincident with the phenomenal development of the automobile industry.

Foreign-born: The composition of the population with respect to proportion of foreign-born has been very different in the two groups of cities. The percentage in the Massachusetts cities from 1900 to 1930 has been nearly twice that for the Michigan group. In table 4 the predominating national groups are shown and the percentages of the total population tabulated. In 1900 from 30 to 40 per cent of the populations of the Massachusetts group were made up of French-Canadian, Irish, English and Portuguese immigrants. The proportions of foreign-born in the census enumerations for these cities since 1900 has steadily decreased but these same groups have predominated. The composition

of the foreign-born population of the Michigan group has been quite different and they have constituted a much smaller proportion of the total populations. The predominating groups of foreign-born have been from the Netherlands, Germany, England and Canada (other than French-Canadian). Poland and Russia have also contributed to the populations of these cities but in relatively small numbers.

Occupations: Data on occupation in both groups of cities have been quite similar in certain respects and radically different in others. In

TABLE 3

Total populations, population per square mile, average number of persons per family in Fall River, Lawrence, Lowell, New Bedford, Flint, Grand Rapids, Pontiac and Saginaw

YEAR	FALL RIVER	LAWRENCE	LOWELL	NEW BEDFORD	FLINT	GRAND RAPIDS	PONTIAC	SAGINAW
				Population				
1870	27,266	28,921	40,928	21,320	5,386	16,507	4,867	7,460
1880	48,961	39,151	59,475	26,845	8,409	32,016	4,509	10,525
1890	74,398	44,654	77,696	40,733	9,803	60,278	6,200	46,322
1900	104,863	62,559	94,969	62,442	13,103	87,565	9,769	42,345
1910	119,295	85,892	106,294	96,652	38,550	112,571	14,532	50,510
1920	120,485	94,270	112,759	121,217	91,589	137,634	34,273	61,903
1930	115,274	85,058	100,234	112,597	153,866	168,592	64,928	80,715
				Population per square mile				
1900	3,089	8,750	6,687	3,293	1,005	5,067	1,302	3,431
1910	3,515	12,013	7,485	4,530	2,956	6,507	1,938	4,083
1920	3,550	13,185	7,941	6,393	7,024	7,956	4,570	5,016
1930	3,396	11,896	7,052	5,938	11,800	9,745	8,656	6,541
				Average number of persons per family				
1900	5.00	4.90	4.90	4.50	4.10	4.30	4.70	4.40
1910	4.90	5.01	4.80	4.60	4.64	4.20	4.74	4.23
1920	4.60	4.80	4.50	4.50	4.70	4.10	4.80	4.20
1930	4.26	3.67	4.21	4.02	4.15	3.87	3.25	3.35

both groups the percentage of males ten years of age and over engaged in gainful occupations has been essentially the same as well as the percentage engaged in manufacturing and industrial pursuits, that is, about 80 and 50 per cent respectively. However, the percentage of females, ten years of age and over, engaged in gainful occupations was much greater in the Massachusetts cities. From 50 to 75 per cent of females engaged in gainful occupations were employed in manufacturing es-

TABLE 4

Per cent of total population classified as foreign-born, and nationality and percentage of predominating groups in Fall River, Lawrence, Lowell, New Bedford, Flint, Grand Rapids, Pontiac and Saginaw

CITY	YEAR	PER CENT OF TOTAL POPULATION CLASSIFIED AS FOREIGN-BORN	NATIONALITY	PER CENT OF TOTAL POPULATION	NATIONALITY	PER CENT OF TOTAL POPULATION	NATIONALITY	PER CENT OF TOTAL POPULATION	NATIONALITY	PER CENT OF TOTAL POPULATION
Fall River	1900	47.7	French-Canadian	19.3	English	11.7	Irish	6.9	Portuguese	2.6
	1910	42.7	French-Canadian	12.8	English	9.2	Portuguese	7.9	Irish	4.3
	1920	35.2	French-Canadian	8.9	English	6.5	Atlantic Islands	5.3	Portuguese	4.7
	1930	27.8	French-Canadian	7.3	English	4.9	Portuguese	4.5	Azores	3.8
Lawrence	1900	45.7	Irish	11.3	French-Canadian	11.2	English	8.2	German	3.9
	1910	48.3	French-Canadian	8.9	Italian	7.8	Irish	6.9	English	6.6
	1920	41.6	Italian	9.0	French-Canadian	6.3	Irish	4.5	English	4.5
	1930	33.7	Italian	7.7	French-Canadian	6.2	English	3.6	Irish	3.5
Lowell	1900	43.1	French-Canadian	15.4	Irish	12.8	Canadian	4.7	English	4.6
	1910	40.9	French-Canadian	11.5	Irish	9.4	English	4.3	Canadian	3.8
	1920	33.8	French-Canadian	9.0	Irish	6.5	English	3.2	Canadian	3.2
	1930	26.1	French-Canadian	7.7	Irish	5.0	Canadian	2.4	English	2.0
New Bedford	1900	40.9	French-Canadian	13.7	English	8.6	Portuguese	7.8	Irish	4.8
	1910	45.2	French-Canadian	12.7	English	9.6	Atlantic Islands	6.7	Portuguese	3.9
	1920	42.1	Atlantic Islands	9.7	French-Canadian	8.1	English	8.0	Portuguese	6.3
	1930	33.2	English	7.2	French-Canadian	6.8	Azores	6.2	Portuguese	4.6
Flint	1900	16.3								
	1910	17.5	Canadian	8.4	English	1.9	German	1.4	Russian	1.1
	1920	16.6	Canadian	5.1	English	1.7	Polish	1.5	Hungarian	1.0
	1930	13.7	Canadian	6.7	German	3.3	English	2.5	Polish	1.6
Grand Rapids	1900	27.3	Dutch	12.6	Canadian	3.8	German	3.7	Irish	1.3
	1910	25.2	Dutch	10.5	German	4.0	Russian	3.1	Canadian	2.6
	1920	20.7	Dutch	8.3	Polish	3.1	Canadian	2.0	German	1.7
	1930	16.2	Dutch	12.6	Polish	5.5	Canadian	3.1	German	3.1
Pontiac	1900	20.7								
	1910	18.4	Canadian	9.8	English	2.9	German	2.2	Irish	1.2
	1920	15.1	Canadian	5.9	English	2.1	German	1.1	Greek	0.6
	1930	14.1	Canadian	6.9	German	3.4	English	2.7	Irish	1.3
Saginaw	1900	27.0	German	11.1	Canadian	8.1	French-Canadian	2.0	English	1.5
	1910	23.2	German	8.7	Canadian	6.5	Russian	1.5	English	1.4
	1920	18.8	German	5.1	Canadian	4.6	Russian	1.7	Polish	1.5
	1930	13.8	German	12.0	Canadian	6.4	Polish	3.7	French-Canadian	2.0

tablishments in these cities while in the Michigan group only a small proportion was similarly engaged.

The type of manufacturing and industurial work in the two groups of cities has been radically different. In the Massachusetts group textile mills furnished occupation for the majority of workers. In Grand Rapids furniture and wood-working factories have employed the greatest proportion of male workers; in Flint and Pontiac automobile manufac-

TABLE 5

Per cent of population ten years of age and over gainfully occupied and per cent engaged in manufacturing and industrial occupations in Fall River, Lawrence, Lowell, New Bedford, Flint, Grand Rapids, Pontiac and Saginaw

	MALES				FEMALES			
	1900	1910	1920	1930	1900	1910	1920	1930
Per cent gainfully occupied								
Fall River	81.9	81.7	83.2	75.7	41.4	41.8	41.6	35.9
Lawrence	84.0	83.7	83.7	75.6	39.0	39.7	43.4	34.9
Lowell	84.3	82.8	82.6	75.3	41.8	41.5	38.7	32.0
New Bedford	81.2	84.1	84.5	76.6	33.4	38.3	42.2	38.0
Flint		89.4	88.3	80.8		19.5	22.3	21.0
Grand Rapids	80.4	81.4	81.0	76.9	21.8	23.9	26.5	25.3
Pontiac			82.7	82.4			20.5	23.7
Saginaw	79.5	80.1	81.0	77.5	21.6	23.9	22.5	23.1
Per cent engaged in manufacturing and industrial occupations								
Fall River	52.5	57.5	55.5	46.9	34.0	32.9	31.6	22.6
Lawrence	55.9	59.9	61.5	49.2	29.5	30.3	34.1	22.1
Lowell	52.8	56.4	55.4	41.9	30.2	29.0	26.3	16.0
New Bedford	49.1	57.1	59.4	46.2	22.8	27.6	31.8	24.6
Flint		64.1	63.4	54.1		4.4	6.2	4.4
Grand Rapids	35.8	44.3	45.5	38.8	5.1	7.3	8.2	4.1
Pontiac			55.4	50.5			3.9	2.8
Saginaw	32.2	38.4	36.5	41.8	5.6	6.6	6.1	4.4

turing has been the predominating industry and in Saginaw there have been various types of industries.

Density of population: Accurate and reliable measurements of crowding in either group of cities are not possible. The number of persons per square mile of land area in a given city is at best only a rough index. If a large part of the land area of a city is used for commercial establishments, factories, transportation facilities, parks, and other nonresidential uses, the ratio of land area to total population may not seem to indicate

crowding. A large part of the population may be housed in a small area under such conditions. In another city with much better housing conditions, the number of persons per square mile may seem to be greater than in the former. In the Massachusetts cities the average number of persons per square mile was very little greater than the number for the Michigan cities.

The average number of persons or families per dwelling for cities is known but these data cannot be regarded as reliable indices of crowding since the type and size of dwellings are not known. A better index of crowding in a city would be the average number of persons per room but such data are not available.

The average size of families gives some suggestion of crowding within family units. In the Massachusetts cities the average number of persons per family has been greater than the average number for the Michigan group.

Housing: From reports of various types of surveys made between 1910 and 1915, it is possible to get a fairly comprehensive picture of housing conditions in all of the cities used in this study except Flint and Pontiac, Michigan.

It is reported that one-family, detached houses prevailed throughout all sections of Saginaw (4). Two-family houses were few in number and generally detached. Row-houses were almost unknown, and tenements and apartments were few in number. The average workingman's house was described as almost invariably a well-kept cottage or bungalow centered in its own plot of ground insuring excellent light and ventilation.

In Grand Rapids (5) the one-family house was the predominating type of dwelling in all sections of the city. Few overcrowded lots were to be found. The worst conditions described were a lack of good and adequate toilet accommodations and lack of sewer and water connections.

In a survey of New Bedford (6) made in 1913 the river section was described as being the poorest, most congested and most dilapidated part of the city. In this section where a large proportion of the population of the city resided, the houses, uniformly old and in disrepair, were principally of three types, mill-house, large block and old residences. In some instances basements were occupied.

In Lawrence (7) it was found that more than one-third of the population lived on one-thirteenth of the city's area, approximately one-half of the families in the city lived in one and two-family houses, and the remainder in houses of three apartments or more. Most of the latter

were of the large block type, and were located in the congested section of the city.

In the early development of Lowell (8) manufacturing corporations built many tenement houses for the use of employees. These corporation, tenement and boarding houses were in the centre of the city, near the mills and were kept in good repair and sanitary condition. Later, when most of these dwellings were sold to individuals and real estate operators, overcrowding and poor sanitary conditions developed. They were occupied, it is said, by the poor and ignorant classes of people. By 1910 bad housing conditions were not confined to one locality, but were scattered in "spots" all over the city. Not only tenement but other dwellings were in what was described as being in an "unwholesome and unsanitary" condition. One tenement had a record of six deaths from tuberculosis in five successive families.

In a survey of housing conditions in Fall River (9) in 1912 the principal problem was found to be the tenement house. It was not confined to a limited territory but extended over a wide area embracing several sections of the city. It was found that congestion of population measured in terms of the average number of persons per room did not constitute as serious a problem as sanitary abuses, such as poor ventilation and lighting, lack of cleanliness and poor facilities for sewage disposal.

DISCUSSION

About ten years ago following several reports on tuberculosis in the city of Boston, Professor E. B. Wilson raised certain objections regarding the validity of the conclusions contained in the reports (10). He suggested six criteria which should be applied to the data before making comparisons of mortality rates in Boston with those of certain other cities. These criteria will be used as a basis of discussion of the material presented in this paper. Professor Wilson suggested that adjustments be made for (*1*) nonresident deaths; (*2*) selectivity of population; (*3*) for race and (*4*) for age; and that allowances be made for (*5*) differences in reporting or editing mortality data and for mistakes and (*6*) for density of population.

Several of these criteria can be disposed of in a few sentences. For instance, the number of deaths from tuberculosis have been corrected for residence in so far as possible. It is felt that any further corrections in this respect would be very small. Selectivity of population refers to cities or areas to which large numbers of patients migrate for treatment

of tuberculosis. The cities used in this study have not been treatment centres for the disease. Since age specific rates have been calculated no adjustment need be made for age. It has been demonstrated that the same differences have existed in age specific rates as in the crude rates for the two groups of cities. There is no way of making any adjustments for errors in reporting or for mistakes, but the probabilities are that such errors have been present to about the same degree in each group of cities. Even allowing for a 10 per cent error would not erase the differences which have existed for the two groups of cities.

This leaves two of the criteria for further discussion. The marked difference in the composition of the populations with respect to foreign-born in the two groups of cities has been clearly shown. Numerous reports have demonstrated that immigrants from certain countries to the United States experience higher tuberculosis death rates than the native-born of native parents. The Irish have had especially high rates. The rates for the French, English, German and Scandanavian immigrants have also been relatively high. On the other hand, Italians, Russians and Jews have had relatively low rates. In Lowell, Massachusetts, (8) from 1880 to 1909 the average tuberculosis mortality rate was 364 per 100,000 population among those classified as Irish, 263 among the French-Canadian, 257 among the English immigrants, and 182 among the native-born. It is not within the scope of this paper to discuss the question whether certain racial or ethnic groups have a greater susceptibility to tuberculosis than other groups or whether the relatively high rates are due to poor environmental conditions in which the immigrants live. It is important to note, however, that the populations of the four Massachusetts cities used in this study have contained a large percentage of racial groups which experience high death rates from tuberculosis in this country. The foreign-born of the Michigan cities have been fewer in number and have been made up of groups which have experienced lower tuberculosis death rates.

The available information on mere density of population as measured by the number of persons per acre or square mile of land area in the two groups of cities is not sufficient to warrant drawing any definite conclusions on the influence of density in determining differences in tuberculosis mortality. The data presented in table 3 indicate a slightly greater concentration of population and somewhat larger family units in the Massachusetts cities. In conjunction with the available informa-

tion on housing conditions, the somewhat greater density of population per square mile of land area and slightly larger families assumes greater significance. Housing conditions found in two of the Michigan and all four Massachusetts cities between 1910 and 1915 have already been described. It is quite evident from the descriptions given that housing conditions which prevailed at that time were more favorable for the spread of tuberculosis in the Massachusetts group than in either Grand Rapids or Saginaw, Michigan.

Although occupation has not been included in the criteria used as a basis of discussion, it warrants brief comment. It has not been proved that any occupation as such predisposes to tuberculosis except where workers are exposed to certain concentrations of silica or chemically similar dusts for comparatively long periods of time. One is not justified in assuming that a given occupation, with the exception just noted, is a predisposing factor to a high tuberculosis death rate merely because the death rate of workers engaged in that occupation is higher than that for workers engaged in other occupations without taking into consideration other factors. It seems more reasonable to assume that environmental, economic and social conditions in which people live and work are more important factors in the production of a high tuberculosis death rate than the type of occupation. Low wages, poor working conditions, crowding in unsanitary dwellings and inadequate food favor the spread and development of tuberculosis regardless of occupation.

CONCLUSION

Tuberculosis mortality rates have been higher in four Massachusetts cities than in a similar group in Michigan. Both groups of cities were approximately the same size according to the 1930 census and a large proportion of population has been engaged in industrial occupations.

It appears that the difference in mortality in the two groups of cities can best be explained on the basis of more unfavorable environmental and social conditions in the Massachusetts groups. It also appears that indirectly the composition of the population with respect to nationality has played some part in these differences in mortality.

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REFERENCES

(1) DAUER, C. C.: Distribution of tuberculosis mortality in the white population of the United States, Public Health Reports, June, 1937, *52*, 70.

(2) DAUER, C. C.: Sex differences in tuberculosis mortality in the United States, Am. Rev. Tuberc., 1938, *37*, 435.

(3) DAUER, C. C.: Sex differences in trends of tuberculosis mortality, Am. J. Hyg., 1938, *27*, 538.

(4) ALLEN, N. F.: Infant mortality: Results of a field study in Saginaw, Michigan (1913), Children's Bureau Publication, No. 52, 1919.

(5) Housing conditions and tendencies in Grand Rapids, Michigan, Report of the Housing Committee of the Charity Organization Society of Grand Rapids, Michigan, 1913.

(6) WHITNEY, JESSAMINE S.: Infant mortality: Results of a field study in New Bedford, Massachusetts (1913), Children's Bureau Publication, No. 68, 1920.

(7) The Report of the Lawrence Survey, Lawrence, Massachusetts, 1912.

(8) KENNGOTT, G. F.: The record of a city: a social survey of Lowell, Massachusetts, Macmillan, New York, 1912.

(9) Housing conditions in Fall River, Associated Charities Housing Committee, 1912.

(10) WILSON, E. B.: Tuberculosis in Boston and elsewhere, Boston Med. & Surg. J., 1927, *196*, 665.

ROUTINE BRONCHOSCOPY IN PATIENTS WITH ACTIVE PULMONARY TUBERCULOSIS[1]

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During the past few years tuberculous involvement of the trachea and bronchi has been recognized to be of clinical importance and has been the subject of an increasing number of articles in the literature (1 to 5). Early in 1935, we believed that the recognition of this complication was important enough to warrant the routine bronchoscopic examination of all patients admitted to a tuberculosis sanatorium. At that time we were discovering instances of tuberculous tracheobronchitis in patients having a wide variety of symptoms and roentgenological findings which we were unable to correlate satisfactorily. It was believed that many cases of tracheal or bronchial involvement were unrecognized among our patients.

Accordingly, routine bronchoscopic examinations were performed on patients admitted to the Michigan State Sanatorium between September 18, 1935, and April 24, 1937. During this period, 376 patients were admitted. The bronchoscopic findings of 272 (73 per cent) of these patients form the basis of this report. The reasons for noninclusion of the remaining 104 patients were as follows: too ill (advanced tuberculosis or other diseases), 33; discharged before bronchoscopy could be performed, 25; childhood type of tuberculosis, 14; ulcerative or stenotic laryngeal disease, 12; no pulmonary tuberculosis, 10; refused bronchoscopy, 8; and bronchoscopy performed prior to admission, 2. It will be noted that the coöperation of the patients was excellent as only 8 refused bronchoscopy. The extent of the pulmonary tuberculosis of the 272 patients who were bronchoscoped was classified on admission as follows: minimal, 36 (13.2 per cent); moderately advanced, 147 (54.1

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per cent); far advanced, 89 (32.7 per cent). The sex was as follows: male, 112 (41 per cent); female, 160 (59 per cent). The average age was 23.7 years, the youngest being eight years and the oldest fifty-nine years.

In order to correlate our bronchoscopic findings with symptoms and roentgenological findings, and in order to determine whether the performance of a bronchoscopy had any deleterious effects in patients with active pulmonary tuberculosis, the following measures were carried out in conjunction with our bronchoscopic examinations:

1: A careful history was obtained with special reference to the symptoms which we had in the past associated with tuberculous tracheobronchitis.
2: Roentgenograms of the lungs were taken within one month before bronchoscopy and at the end of a three-week period following bronchoscopy.
3: Indirect laryngeal examinations were made (by the same examiner) (*a*) during the week previous to bronchoscopy, (*b*) one week following bronchoscopy, and (*c*) three weeks following bronchoscopy.
4: Sputum examinations were made by smear, concentrate or culture, as indicated, on 48 hour specimens obtained (*a*) during the week previous to bronchoscopy and (*b*) during the 48 hours following bronchoscopy.
5: The patients' temperatures were recorded at four-hour intervals for one week before and one week after bronchoscopy.

A complete analysis of our findings will not be given in this paper. We shall confine our discussion to the following topics: (*1*) the bronchoscopic findings, (*2*) a correlation of symptoms, roentgenological and bronchoscopic findings, (*3*) a discussion as to the value of routine bronchoscopic examinations in the discovery of significant tuberculous lesions of the trachea and bronchi and (*4*) the effect of bronchoscopic examinations on patients with active pulmonary tuberculosis.

A detailed analysis of the cases exhibiting bronchscopic evidence of tuberculous tracheobronchitis is planned in a subsequent report. Most of these patients, together with other known cases, have been followed by one or more bronchoscopic examinations, subsequent to the initial examination.

BRONCHOSCOPIC FINDINGS

An analysis of our bronchoscopic findings appears in table 1. It will be noted that 30, or 11 per cent, of our patients showed definite evidence of tuberculous involvement of the trachea or bronchi. The

diagnosis in all cases was based on the bronchoscopic appearance of the lesion. We hesitate to take biopsies except in cases where a differential diagnosis must be established because we feel that this procedure is not always safe.

Our criteria for the classification of these lesions as to type were as follows: (*1*) *Submucosal*: diffuse or circumscribed infiltration or thickening but with unbroken mucosa. This type of lesion may produce a soft stenosis. (*2*) *Tuberculoma*: isolated, irregular, projecting or pedunculated tumors which may or may not be entirely covered by mucosa. (*3*) *Ulcerative*: lesions of the bronchial wall, either localized or diffuse, with definitely broken mucosa, sometimes containing a white membrane of purulent exudate, and often containing exuberant granulation tissue. (*4*) *Fibrostenotic*: cicatricial narrowing of tracheal or

TABLE 1

Bronchoscopic findings (272 patients)

FINDINGS	PATIENTS	PER CENT
Negative	177	64.8
Tuberculous involvement	30	11.0
Mucosal congestion (probably nonspecific infection)	30	11.0
Distortion, kinking or scarring	21	7.9
Questionable tuberculous involvement	13	4.9
Bronchogenic carcinoma	1	0.4
	272	100.0

bronchial lumen, probably the result of healing of an ulcerative lesion. (*5*) *Ulcerostenotic*: lesions which represent an intermediate stage between (*3*) and (*4*). The number of cases of each type together with the severity of the lesions, based on their bronchoscopic appearance, is given in table 2.

Subsequent bronchoscopic examinations were performed upon 7 of the 13 patients classified as having questionable tuberculous involvement. In 6 patients, the lesions disappeared or improved greatly and were not believed to be tuberculous; the seventh patient later showed definite evidence of tuberculous bronchitis.

The bronchogenic carcinoma found in one patient was associated with far advanced pulmonary tuberculosis.

In a group of 90 patients who were bronchoscoped routinely before thoracoplasty, Warren, Hammond and Tuttle (5) found 12 (13.3 per

cent) having bronchial ulceration. In a series of 122 cases of pulmonary tuberculosis studied at autopsy, Bugher, Littig and Culp (1) found that 50 (41 per cent) showed tuberculous lesions of the trachea, main bronchi or both. These two groups are not entirely comparable to ours, since patients with far advanced lesions evidently predominated in both. Only 32.7 per cent of our patients were classified as far advanced.

TABLE 2

Bronchoscopic classification of tuberculous tracheobronchial lesions according to type and severity (30 patients)

TYPE	PATIENTS	SEVERITY	PATIENTS
Submucosal	7	Mild	10
Tuberculoma	2	Moderate	9
Ulcerative	5	Severe	11
Fibrostenotic	12		
Ulcerostenotic	4		
	30		30

TYPE	SEVERITY	PATIENTS
Submucosal	Mild	5
Submucosal	Moderate	2
Tuberculoma	Mild	2
Ulcerative	Mild	2
Ulcerative	Moderate	2
Ulcerative	Severe	1
Fibrostenotic	Mild	1
Fibrostenotic	Moderate	5
Fibrostenotic	Severe	6
Ulcerostenotic	Severe	4
		30

CORRELATION OF SYMPTOMS, ROENTGENOLOGICAL AND BRONCHOSCOPIC FINDINGS

Among the symptoms most frequently associated with tuberculous tracheobronchitis are: (*1*) an *oral wheeze;* (*2*) *asthmatoid attacks;* (*3*) *difficult expectoration,* frequently associated with paroxysms of violent coughing; (*4*) *sputum irregularities,* often consisting of an excessive amount of sputum for the degree of pulmonary involvement, also marked daily variations in the amount of sputum, and, occasionally, exceptionally tenacious sputum; (*5*) an *obstruction* or *retention syndrome,*

characterized by an intermittent fever not explained by the activity of the pulmonary lesion, a severe brassy cough, the sputum irregularities mentioned above, otherwise unexplained attacks of dyspnoea and by symptoms of toxic absorption.

Forty-one (15.4 per cent) of our patients exhibited one or more of the symptoms listed above (see table 3); 16 of these patients had positive bronchoscopic evidence of tuberculous tracheobronchitis. The remaining 231 (84.6 per cent) patients had none of the characteristic symptoms, although 14 of them were found to have definite tuberculous involvement of the tracheobronchial tree.

The symptoms of 5 patients could be accounted for by nontuberculous compression or kinking of the tracheobronchial tree. The symptoms of one patient were due to the obstruction produced by a bronchial tumor.

TABLE 3

Analysis of symptoms (41 patients)

SYMPTOMS	PATIENTS	PATIENTS WITH TUBERCULOUS TRACHEOBRONCHITIS
Oral wheeze	34	13
Difficult expectoration	19	6
Sputum irregularities	15	5
Asthmatoid attacks	8	3
Obstruction syndrome	8	4

It will be noted that a persistent oral wheeze was the most common symptom encountered.

The following roentgenological findings have been formulated by correlation of our roentgenograms with our bronchoscopic findings:

I. *Findings or changes frequently associated with tuberculous tracheobronchitis:*

(1) Definite lobar (figures 1A and B) or total (figures 2C and 3B) pulmonary atelectasis with or without collapse therapy. This may be intermittent in character (figures 2A, B and C). Complete pulmonary atelectasis (figures 3A and B) sometimes follows induction of pneumothorax even though the pulmonary lesion is confined to one lobe.

(2) Tendency to unexpected or unexplained spreads of tuberculous parenchymal infiltration which may appear and disappear suddenly.

(3) Evidence of a partially obstructed cavity with a fluid level usually present (figure 4). Cavity often exhibits rapid enlargement which cannot be satisfactorily explained on the basis of tissue destruction.

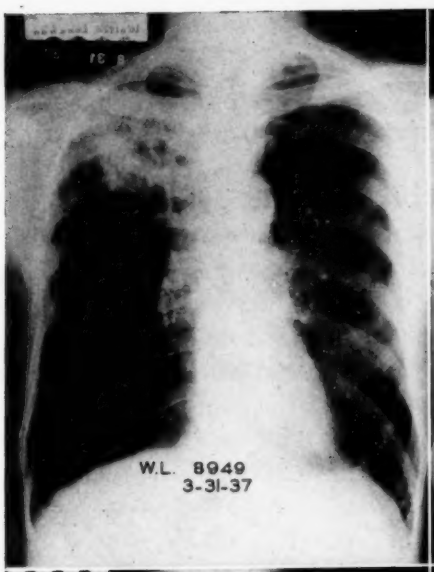


FIG. 1A

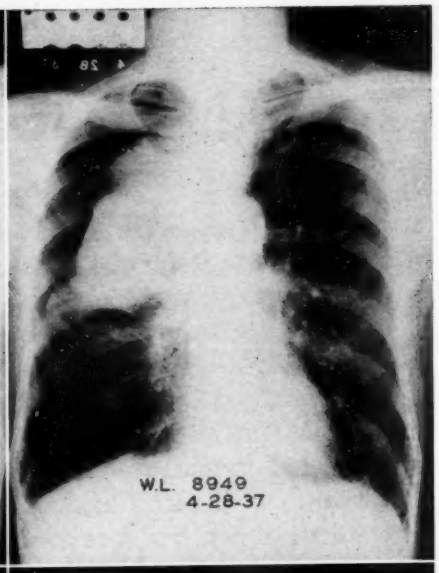


FIG. 1B

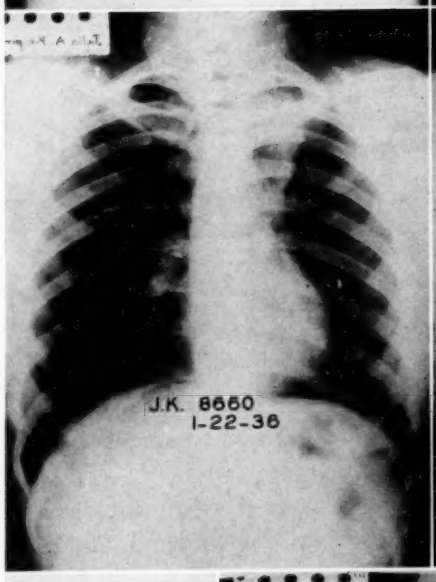


FIG. 2A

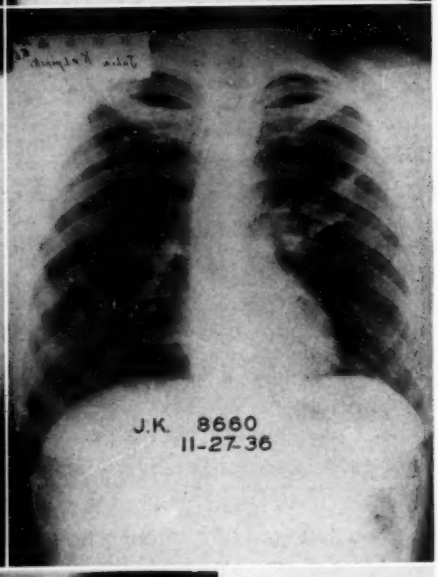


FIG. 2B

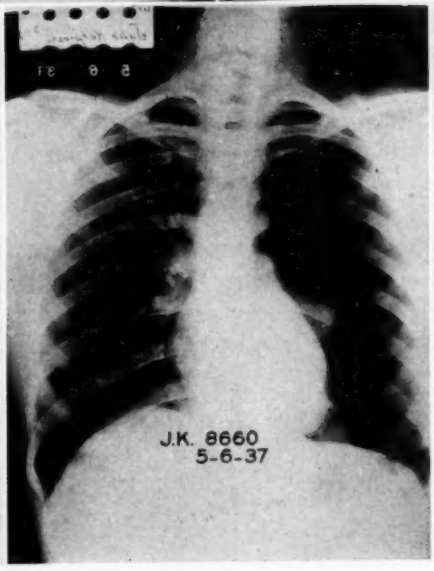


FIG. 2C

II. *Findings occasionally associated with tuberculous tracheobronchitis:*

Shadows possibly representing atelectasis but in which the differential roentgenological diagnosis cannot be made with certainty between atelectasis, dense pulmonary infiltration, pleural effusion, etc. (suspicious atelectasis).

III. *Findings which may happen to be associated with tuberculous tracheobronchitis:*

Dense obscuration (figure 5) of pulmonary field definitely caused by pleural thickening, pleural fluid, complete collapse by pneumothorax or thoracoplasty, or paraffin filling after extrapleural pneumonolysis.

The number of our patients exhibiting these findings is given in table 4.

It will be seen that some degree of pulmonary atelectasis was the most frequent finding associated with tuberculous tracheobronchitis.

TABLE 4

Analysis of roentgenological findings associated with tuberculous tracheobronchitis (272 patients)

ROENTGENOGRAM	PATIENTS	PATIENTS WITH TUBERCULOUS TRACHEOBRONCHITIS
No characteristic findings	213	7
Definite atelectasis	26	16
Suspicious atelectasis	18	4
Unexpected spreads	6	4
Dense obscuration of pulmonary field	8	3

The sudden complete pulmonary collapse which sometimes developed after the induction of a pneumothorax, even though the pulmonary disease had been confined to one lobe, interested us particularly (figures

FIG. 1A. W. L. March 31, 1937. Infiltration and cavity right upper lobe. No bronchoscopy.

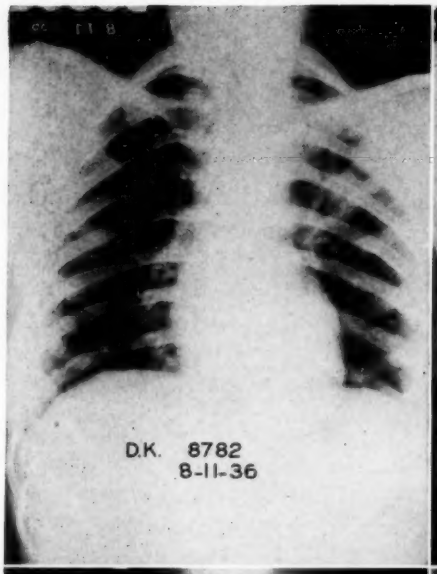
FIG. 1B. W. L. April 28, 1937. Atelectasis right upper lobe following induction of pneumothorax. Bronchoscopy: marked fibrostenosis right upper lobe orifice. (Fifteen of 22 cases showing definite atelectasis under pneumothorax, as illustrated, were found to have tuberculous tracheobronchial lesions.)

FIG. 2A. J. K. January 22, 1936. Atelectasis of left upper lobe. Bronchoscopy: no lesion in trachea or visible bronchi; tuberculous bronchitis possibly present in small invisible branches.

FIG. 2B. J. K. November 27, 1936. Left upper lobe areated. Bronchoscopy: negative.

FIG. 2C. J. K. May 6, 1937. Left pneumothorax with dense homogeneous shadow representing total atelectasis of left lung. Manometric reading: −3 −1. Bronchoscopy: extensive ulceration left main bronchus and orifice of left upper lobe bronchus; narrowing of main bronchial lumen 1 cm. below carina.

FIG. 3A



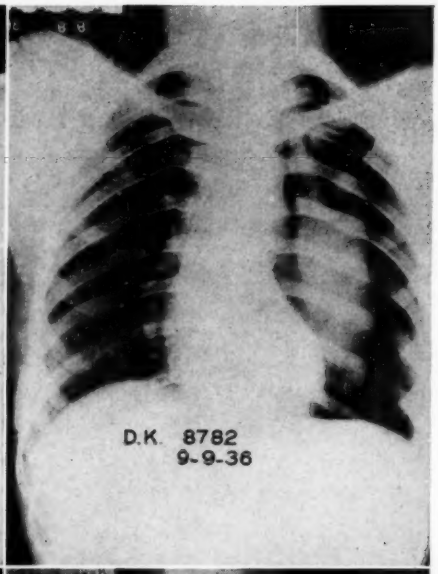
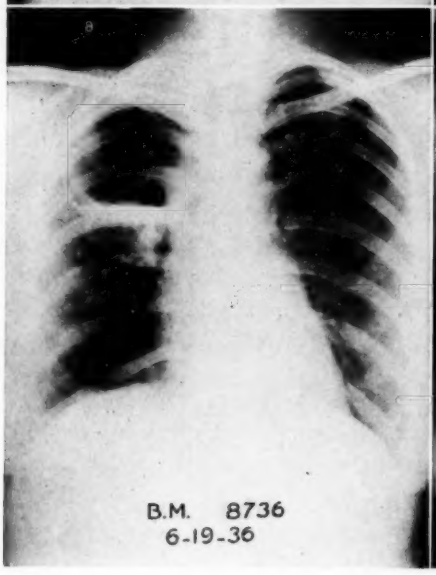


FIG. 3B

FIG. 4



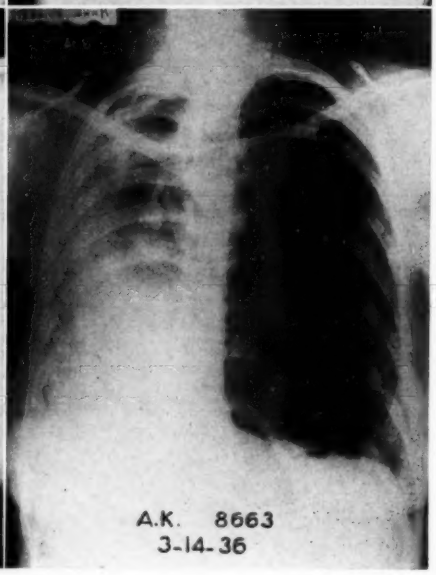


FIG. 5

FIG. 3A. D. K. August 11, 1936. Moderate infiltration and cavity left upper lobe; no atelectasis; no bronchoscopy.

FIG. 3B. D. K. September 9, 1936. Sudden atelectasis five days following induction of pneumothorax; manometric reading before refill on September 9, 1936, −13 −6; after 300 cc. of air, −9 −1. Bronchoscopy: ulcerative tuberculous bronchitis involving left main bronchus just below carina.

FIG. 4. B. M. June 19, 1936. Large cavity right upper lung. (Patient had constant wheeze and evidence of partially and intermittently obstructed cavity.) Bronchoscopy July 27, 1936: stenosis of right main bronchus 0.5 cm. below carina; 3 mm. opening; no ulceration.

FIG. 5. A. K. March 14, 1936. Obscuration of right lung field; arrow points to carina. Bronchoscopy March 16, 1936: complete stenosis of right lower lobe bronchus; no ulceration.

3A and B). We found that this particular type of collapse was frequently, but not always, associated with bronchial involvement.

Of the 21 patients having abnormal bronchoscopic findings consisting of distortion, kinking or scarring of the tracheobronchial tree (table 1), the roentgenograms of only 4 exhibited the findings sometimes associated with definite tuberculous tracheobronchitis.

Eighteen of our 272 patients had no roentgenological evidence of active pulmonary tuberculosis and yet had positive sputa. All the patients in this group had what appeared to be a complete and satisfactory pulmonary collapse by pneumothorax or thoracoplasty. Nine (50 per cent) of these patients had bronchoscopic evidence of tuberculous tracheobronchitis. Since we know that our present day methods of roentgenological diagnosis are not infallible, we cannot assume that the tuberculous tracheal or bronchial lesions of these patients were necessarily the source of the bacilli.

Correlation of symptoms and roentgenological findings: One hundred and ninety-four patients exhibited no symptoms or roentgenological findings suggestive of tuberculous tracheobronchitis; 6 of these patients were found to have insignificant tuberculous tracheal or bronchial lesions, all of which are classified as mild in table 2.

Twenty-six patients had both suggestive symptoms and roentgenological findings; 15 of these patients had tuberculous tracheobronchitis.

Thirty-three patients exhibited suggestive roentgenological findings but had no suggestive symptoms; 8 of these patients had tuberculous tracheobronchitis.

Nineteen patients presented suggestive symptoms alone; only one of them had a tuberculous bronchial lesion.

THE VALUE OF ROUTINE BRONCHOSCOPIC EXAMINATIONS

Instances of tuberculous tracheobronchitis were found during the course of these routine bronchoscopic examinations which would not otherwise have been discovered. This is especially true for the first part of our series of patients. As we began to correlate our symptoms, roentgenological findings and bronchoscopic findings, we were able to predict much more accurately before bronchoscopy which patients were likely to have tracheal or bronchial involvement.

In retrospect, we find that if we had not bronchoscoped these patients who exhibited no suspicious symptoms or roentgenological findings (71.3 per cent of the total) we would have failed to discover only 6

insignificant bronchial lesions. In order to verify the insignificance of these lesions, 5 of these patients were subsequently bronchoscoped within approximately three months of the initial examination. The sixth lesion was discovered near the end of our series and sufficient time had not elapsed to permit a follow-up examination. The lesions of 4 of these 5 were found to have disappeared entirely (without local treatment). The fifth lesion (a pin-head size submucosal tubercle) was unchanged at the time of the second examination but was so small that further follow-up seemed unnecessary.

We feel, therefore, in the light of our present knowledge, that the routine bronchoscopic examination of patients with active pulmonary tuberculosis is unnecessary for the discovery of significant tuberculous lesions of the trachea and bronchi. We now bronchoscope only those patients presenting definite roentgenological or symptomatic indications.

In retrospect, we consider that 78, or 28.7 per cent, of our 272 patients presented one or more indications for bronchoscopy. Twenty-four of these patients had bronchoscopic evidence of tuberculous tracheobronchitis.

It will be noted that the roentgenological findings are the most reliable single diagnostic aid. Any patient, however, whose roentgenogram exhibits any suspicion of the characteristic findings, or who exhibits any of the characteristic symptoms, or who has positive sputum without roentgenological evidence of active pulmonary disease must be bronchoscoped if significant tuberculous tracheal and bronchial lesions are not to be overlooked.

THE EFFECT OF BRONCHOSCOPY

The following analyses were made in order to determine whether bronchoscopy had had a deleterious effect upon any of our patients.

Roentgenological examinations: An increase in the pulmonary disease of only 4 patients was evident on comparison of the prebronchoscopic and postbronchoscopic roentgenograms. None of these changes were serious in nature. In two cases, the increase was represented by minimal infiltrative lesions; in one case, by a slightly enlarged cavity with slight additional infiltration; and in the fourth case, by a small pleural effusion. We do not consider that the bronchoscopic examination can be blamed for these increases, since we believe that a similar number of changes can be expected in the roentgenograms of any comparable group of patients with active pulmonary tuberculosis in a corresponding period of time (from four to seven weeks).

Laryngeal examinations: A considerable personal equation was necessarily involved in the interpretation of the indirect laryngeal examinations. However, since the same examiner performed the prebronchoscopic and the two postbronchoscopic examinations, the personal error was reduced to a minimum. Bronchoscopies were not performed in the presence of ulcerative or severe stenotic laryngitis. Such findings were considered to contraindicate the examination in 12 patients.

The results of the prebronchoscopic laryngeal examinations of our 272 patients were as follows: negative, 157; definitely tuberculous, 47; nonspecific infection, 47; questionably tuberculous, 20; and syphilitic, 1. The following temporary postbronchoscopic increases were encountered in 45 patients (16.1 per cent): nonspecific, 24; slight traumatic, 10; slight tuberculous, 5; moderate traumatic, 3; and moderate tuberculous, 3. No lasting severe tuberculous, traumatic or nonspecific increase in the laryngeal findings was encountered. The traumatic increases consisted principally of a slight injection of the vessels of the vocal cords which, in most instances, had disappeared by the time of the second postbronchoscopic examination. In 3 cases, small tags appeared on the true cords. Two of these persisted for several weeks and one for two months. All finally disappeared leaving only small nodules or scars. These changes were classified as moderate traumatic increases. Extensive oedema did not appear in any case following bronchoscopy and no tracheotomies were necessary.

Sputum examinations: In some cases the quantity of sputum was increased temporarily for a few days after bronchoscopy. This additional sputum was light in character. An analysis of the prebronchoscopic and postbronchoscopic examinations for tubercle bacilli demonstrated no significant changes. Of 136 patients having negative prebronchoscopic sputum cultures, 19 had positive postbronchoscopic examinations by concentrate or culture. Of the other 136 patients having positive prebronchoscopic sputum examinations, 10 became negative on culture after bronchoscopy.

Temperature changes: The temperature curves of 222 of the 272 patients showed no change following bronchoscopy. Temporary rises of from one to three degrees occurred in 32 patients, and a lower temperature curve was noted in 17 patients. We do not regard these changes as significant.

After an analysis of our roentgenological findings, laryngeal findings, sputum examinations and temperature changes, we conclude that bronchoscopy had a deleterious effect upon no patient in this group.

SUMMARY AND CONCLUSIONS

1. Routine bronchoscopic examinations were performed upon a representative group of 272 sanatorium admissions with active pulmonary tuberculosis.

2. Thirty, or 11 per cent, of the 272 patients were found to have tuberculous involvement of the trachea or bronchi.

3. Nearly one-third of the entire group of patients had signs or symptoms suggestive of tuberculous tracheobronchitis and in approximately one-third of these definite tuberculous involvement of the trachea or bronchi was found.

4. It is concluded that routine bronchoscopic examination is not necessary for the discovery of significant tuberculous tracheal and bronchial lesions. Bronchoscopy should be performed, however, when certain suggestive signs or symptoms are present if significant tracheal or bronchial lesions are not to be overlooked.

5. Bronchoscopy was found not to have had a deleterious effect upon any patient in this group.

REFERENCES

(1) Bugher, J. C., Littig, J., and Culp, J.: Tuberculous tracheobronchitis: Its pathogenesis, Am. J. M. Sc., 1937, *193*, 515.

(2) Samson, P. C., Barnwell, J. B., Littig, J., and Bugher, J. C.: Tuberculous tracheobronchitis, J. A. M. A., 1937, *108*, 1850.

(3) Barnwell, J. B., Littig, J., and Culp, J.: Ulcerative tuberculous tracheobronchitis, Am. Rev. Tuberc., 1937, *36*, 8.

(4) Kernan, J. D.: Bronchoscopy in pulmonary tuberculosis, Laryngoscope, 1937, *47*, 777. (Extensive Bibliography)

(5) Warren, W., Hammond, A. E., and Tuttle, W. M.: The diagnosis and treatment of tuberculous tracheobronchitis, Am. Rev. Tuberc., 1938, *37*, 315.

DIAGNOSTIC BRONCHOSCOPY IN OCCULT TUBERCULOSIS[1]

SIDNEY J. SHIPMAN

To those who have watched the development of new diagnostic and therapeutic procedures in tuberculosis over the past quarter century, the increasing importance of the bronchoscope in the investigation of intrapulmonary and bronchial conditions has been phenomenal. Firmly established in the diagnosis and treatment of nontuberculous conditions such as benign and malignant tumors, bronchiectasis, abscess and the like, it has within the past few years come to occupy a place of increasing importance in the recognition and possibly in the treatment of tracheobronchial tuberculosis and its sequelae. The admirable work of Samson (1, 2), Tuttle, and Myerson has emphasized this. It is also probable, however, that bronchoscopy has a distinct rôle to play in the diagnosis of occult intrathoracic tuberculosis, a condition in which it has not been employed to the extent that it deserves.

Shortly after the World War, tuberculosis workers in general were occupied with the question of activity in tuberculosis, what it meant, how one arrived at it, and in general were occupied with diagnostic criteria. In particular, the Saranac group laid down five cardinal points in the diagnosis of pulmonary tuberculosis, the most important of which was the finding of tubercle bacilli in the sputum. Cardinal, but of less importance, were a history of haemoptysis of a dram or more, substantiated pleurisy, particularly pleurisy with effusion, râles after cough and a parenchymal lesion by X-ray having the characteristics of tuberculosis. Sputa were collected for days, concentrated in various manners and exhaustively searched. But in many cases presenting themselves with pleurisy, haemoptysis, obstinate cough and the like, no sputum was obtainable. In some of these we now know it is possible to demonstrate tubercle bacilli in gastric washings, when the latter are injected into guinea pigs, thus establishing the diagnosis in a certain number of cases

[1] From the Department of Medicine and the Department of Thoracic Surgery, Dr. Harold Brunn, Director, University of California Medical School, and the University of California Tuberculosis Service, San Francisco Hospital, Department of Public Health, Dr. J. C. Geiger, Director, San Francisco, California.

where it would remain presumptive otherwise. Even so there still remains a not inconsiderable number of patients whose intrapulmonary disease while obvious, as from haemorrhage, nevertheless remains obscure as to exact aetiology. It is the purpose of this report to present three such patients, in whom the diagnosis was cleared up by bronchoscopy and in whom the X-ray films were entirely negative or misleading, two of whom were supposed to be suffering from disease other than tuberculosis.

Case 1: Haemoptysis presumably of tuberculous origin but with negative X-ray films and sputum, and without physical signs.

P. C., a male, age 27, a clerk by occupation (H235890), entered the San Francisco Hospital July 10, 1938, complaining of dyspnoea and pain in the chest for six months and recent haemoptysis. The family history revealed that the patient's sister had had haemoptysis but had never been found to have definite tuberculosis. The patient's wife had died of pulmonary tuberculosis a few years ago. The past history was essentially negative. Two weeks before entry the patient had had a severe coughing attack, which was followed by a brisk haemoptysis of one pint. The patient was sure the blood came from his right side. He entered a general hospital but signed himself out after four days without a definite diagnosis. Following this the patient noticed increasing fatigue and dyspnoea. On the night before entering the San Francisco Hospital he was awakened from sleep spitting up blood. X-ray films were negative. When the patient entered the Tuberculosis Division of the San Francisco Hospital his temperature, pulse and respirations were entirely normal. Two weeks after entry he again had a brisk haemoptysis. Following this he was bronchoscoped by Dr. Alfred Goldman, and in the posterior division of the right lower lobe bronchus there appeared to be some reddening of the mucosa. A smear taken from this bronchus and examined directly revealed numerous acid-fast bacilli.

Here bronchoscopy was not only of great aid in definitely establishing the diagnosis but was extremely useful in localizing the site of the lesion.

Case 2: Persistent, annoying cough with negative X-ray films and no sputum.

W. W., a woman of 66, appearing rather old for her age, who had always been a housewife and whose family history and past history were entirely negative as far as tuberculosis was concerned, was seen by Dr. William Bender in April, 1937 because of persistent, annoying cough which kept her awake. This cough had been present since October, 1936 and had been unrelieved by any of the simpler measures. Doctor Bender referred her for bronchoscopy. This was done at the Thoracic Surgery Clinic of the University of California

Hospital on July 28, 1937. The bronchoscopy revealed an essentially negative larynx, trachea and major bronchi. When the inset tube was inserted into the right stem bronchus, however, there was a little bleeding here and there, rather more than one would expect from what slight trauma might have occurred in a normal bronchus from the passage of the tube. Careful aspiration failed to reveal any particular bleeding point. However, the wall of the right stem bronchus was swabbed and smears and cultures made from this swab with the idea that the woman might be suffering from a fungus infection. The smears were returned negative for fungi but positive for acid-fast bacilli.

Although the X-ray films were entirely negative and the report on the smears was a surprise to everyone concerned, this patient was put to bed for six weeks; her cough disappeared and she felt perfectly well until June, 1938, when her cough returned and she saw Dr. Chesley Bush of Livermore. On getting her past history he returned her to San Francisco, where sputum specimens were now frankly positive and an X-ray film revealed what appeared to be some tuberculous infiltration in the middle lobe of the right lung. In spite of the patient's age, her right lung was compressed and she was treated as an ambulatory patient. Following compression her sputum became negative.

It should be noted that bronchoscopy was done in this case because the patient's age and negative X-ray film suggested a possible bronchial growth as the cause of the cough. It also illustrates the advisability of making bronchial smears even though there appears to be no obvious secretion.

Case 3: Basilar bronchial stenosis with peripheral tuberculosis.

C. F., a white nurse of 27 years of age, appeared for examination September 10, 1936. Her family history was negative except that her father had had asthma, and her past history was essentially negative as far as the chest was concerned. In the summer of 1935 she noticed an insidious cough and some loss of weight. In October, 1935 she noticed some wheezing, which was localized to the lower right chest. She was given adrenalin for this without much relief, and her sputum was repeatedly examined and was always negative for tubercle bacilli. Lipiodol injections were done and the patient was said to have bronchiectasis at the right base. Physical examination revealed wheezing at the right base posteriorly; otherwise it was negative. Bronchograms taken by her previous physician revealed no definite bronchiectatic collections in the right lower and middle lobes but did show a distinct stenosis of the right stem bronchus just above the middle lobe opening. Examination of the sputum was negative for tubercle bacilli. She was taken to the Thoracic Surgery Clinic of the University of California Hospital, where she was bronchoscoped on September 11, 1936. At bronchoscopy the larynx, trachea and left stem bronchus were found to be normal. Just above the right middle lobe bronchial opening there was a circular scar which produced distinct stenosis

above the right middle and lower lobes, behind which sputum apparently accumulated. The stenotic area was dilated somewhat and secretions aspirated distal to the stenosis. This material was found to contain tubercle bacilli. Sanatorium treatment with artificial pneumothorax and phrenic crushing did not relieve the patient, whose unfavorable course was obviously influenced by the stenotic bronchus. Inasmuch as there was no other evidence of tuberculosis, the upper lobes being perfectly clear, it was decided to remove the right lower and middle lobes and the stem bronchus at a point proximal to the area of stenosis. This was done on July 12, 1937, by Dr. Harold Brunn. The patient has now recovered except for a small, draining sinus in the right chest. Moreover, examination of her sputum and the sinus discharge is negative for tubercle bacilli.

This patient was thought to have had bronchiectasis at the right base. When tubercle bacilli were recovered from smears taken beyond the area of bronchial stenosis, the finding was a complete surprise. This case again illustrates the value of smears made at the time of bronchoscopy.

SUMMARY

Three cases are presented to illustrate the diagnostic value of bronchoscopy in certain occult cases of tuberculosis, the diagnosis of which might otherwise remain in doubt. This diagnostic use of bronchoscopy is illustrated by a patient with haemoptyses with negative X-ray films, one with persistent cough with negative X-ray films and in an unusual case of suspected bronchiectasis with localized wheezing and bronchial stenosis. The diagnostic use of bronchoscopy in these cases is not only for the purpose of establishing the aetiology of the condition but, in the presence of negative X-ray films, in accurately localizing the disease process. The conclusion seems obvious that bronchial smears are of great value in establishing a diagnosis of tuberculosis in certain obscure cases.

REFERENCES

(1) SAMSON, P.: Tuberculous tracheobronchitis, The rôle of bronchoscopy, Am. Rev. Tuberc., 1936, *34*, 671.

(2) SAMSON, P., LITTIG, J., BARNWELL, J., AND BUGHER, J.: Tuberculous tracheobronchitis, J. A. M. A., 1937, *108*, 1850.

POSTMORTEM INCIDENCE OF TUBERCULOUS TRACHEOBRONCHITIS[1,2]

I. J. FLANCE AND P. A. WHEELER

In 1879 Heinzi (quoted by Burgher) mentioned the occurrence of tracheal ulcers in pulmonary tuberculosis, but it was in the following year that Eppinger (1) fully described the occurrence of such lesions in autopsy specimens. He found tracheal ulcers occurring in one-eighth of cases without laryngeal tuberculosis and stated that they were preponderantly found in the lower portion of the trachea. Since Eppinger, except for isolated reports of cases, very little appeared in the literature concerning tracheobronchitis of tuberculous origin until 1924. In that year, Heaf (2) reported a series of 133 autopsied cases of pulmonary tuberculosis and found the trachea to be involved in 44 per cent. The lesions he described varied from oedema of the surface to ulceration. He stated that the mucous membrane becomes congested until it is a deep purple in color and then the surface begins to desquamate and ulcers are formed. Then in 1929, Minkovsky (3) in a very excellent paper published the results found in 2,379 autopsied cases of pulmonary tuberculosis. He found the trachea involved in 11.48 per cent of the total; 3 per cent were without laryngeal findings and the remainder, 8.48 per cent, were present concomitantly with laryngeal tuberculosis. The lesions were most frequently present in the lower part of the trachea, but, contrary to previous views, were not found preëminently on the posterior surface. Minkovsky also quotes other authors and states that their findings of tuberculous tracheobronchitis in autopsy series varied from 0 per cent of the Italian, Loui, to 25 per cent of the Russian, Dobromilsky.

In 1934, Eloesser (4) discussed stenotic lesions of the trachea and bronchi in cases of pulmonary tuberculosis. Following Eloesser, in 1934, Reichle and Frost (5) discussed the subject of ulcerative tracheobronchitis from the point of view of pathogenesis. They observed

[1] From Robert Koch Hospital, Koch, Missouri, and St. Louis City Hospital, Hospital Division, Department of Public Welfare, St. Louis, Missouri.

[2] Presented at a meeting of the St. Louis Trudeau Club, St. Louis, Missouri, May, 1938.

that, since most of their cases showed tubercles in close association with the submucosal mucous glands, infection was carried from the lung to these glands and thence to the bronchial mucosa. They named this process, infection by contiguity, and felt that this was the prime method of tuberculous infection of the trachea and bronchi. Two other methods of infection, by implantation, occurring in the lower lobe branches, and by continuity, occurring in upper lobe involvement, were felt by them to be distinctly secondary in importance. Following Reichle and Frost, several clinical papers appeared, most of them concerned with the incidence, as determined by bronchoscopic appearance and treatment of tracheobronchial ulceration. Among these are papers by Samson (6), Barnwell, Littig and Culp (7), and Warren, Hammond and Tuttle (8). The authors are all in agreement as to the incidence of tracheobronchial ulcerations, approximating it at 10 to 15 per cent, as determined by bronchoscopy, and all also agree as to the symptom complex resulting from these lesions which may lead one to suspect their presence. These are marked wheezing, dyspnoea, cyanosis and changes in type and amount of sputum. Warren, *et al.* state that, in a group of cases presenting these symptoms, 57.5 per cent were found to have bronchial ulcerations or stenosis or both. The most recent paper has been one by Burgher, Littig and Culp (9), in which the pathological aspect of tuberculous tracheobronchitis is discussed. In a series of 122 autopsies on cases of pulmonary tuberculosis they found tuberculous involvement of the trachea in 20.5 per cent, and of the bronchi in 33.6 per cent of the cases on microscopical examination. The authors do not state in how many cases gross lesions were discernible, but only state that in case no gross lesion was present routine sections were taken. They found the ulcers more frequently posteriorly, and felt that tracheal involvement was a matter of implantation or contact infection from the lung.

For the past three years we have been interested in this problem and accordingly have carefully examined at autopsy the trachea and bronchi down to the third order, on all our cases of pulmonary tuberculosis. The trachea was usually removed well above the arch of the aorta and intact with the remainder of the respiratory tree. For the past year, however, we have removed the entire respiratory tree intact from the larynx downward. The trachea and bronchi were opened posteriorly in the line of deficiency of the cartilages. We were interested in the

occurrence of gross ulcerations in the trachea and bronchi so that if any such lesions, or even slightly suspicious lesions, were encountered, sections were made for microscopical study. No sections were taken routinely if no lesions were demonstrable on gross inspection.

During these three years, 285 cases of pulmonary tuberculosis have come to autopsy, cases on which the trachea and bronchi were examined as stated above. In this series 9 cases of gross tuberculous tracheobronchitis, proved by microscopical study, were found, a total incidence of 3.1 per cent. Of these 9 cases, 7 were tracheal ulcers, one was a case of ulceration of the left main bronchus associated with stenosis of the same, and the ninth case was one in which no ulcerations were seen, but only submucosal tubercles.

All our cases died with far advanced tuberculosis with cavitation. Tuberculous involvement of other organs was rather extensive insofar as 7 cases showed involvement of the larynx, intestine and liver; 6 showed involvement of the spleen. The kidney and peritoneum were involved in one case each. Amyloid disease of the liver, spleen, kidney and adrenals was present in the case of submucosal tubercles of the bronchi without ulceration.

Four males and 5 females comprise this group of 9 cases and, although this series is small, it is interesting to note that the average age at death for the males was 40.5 years, while that of the females was 30.2 years.

As to clinical symptoms we can only say that, on checking through the clinical histories of the cases at hand, none presented any symptoms of marked wheezing, dyspnoea, cyanosis or sputum changes, other than those attributable to a moribund state. It may be stated here that fairly accurate clinical records and charts had been kept on all the patients making up this group.

CONCLUSIONS

1. A series of 285 autopsied cases of pulmonary tuberculosis is presented.

2. Tuberculous tracheobronchitis was present grossly in 9, or 3.1 per cent of the cases.

REFERENCES

(1) EPPINGER: Klebs. Handbuch der pathol. Anat., 1880, Bd. 2, p. 293.
(2) HEAF: Lancet, October 4, 1924.
(3) MINKOVSKY: Laryngoscope, 1929, *39*, 819.

(4) ELOESSER, L.: Bronchial stenosis in pulmonary tuberculosis, Am. Rev. Tuberc., 1934, *25*, 123.
(5) REICHLE, H. S., AND FROST, T. T.: Am. J. Path., 1934, *10*, 651.
(6) SAMSON, P. C.: Tuberculous tracheobronchitis, Am. Rev. Tuberc., 1936, *34*, 671.
(7) BARNWELL, J. B., LITTIG, J., AND CULP, J. E.: Ulcerative tuberculous tracheobronchitis, Ibid., 1937, *36*, 8.
(8) WARREN, W., HAMMOND, A. E., AND TUTTLE, W. M.: Ibid., 1938, *37*, 315.
(9) BURGHER, J., LITTIG, J., AND CULP, J.: Am. J. M. Sc., 1937, *193*, 515.

TUBERCULOUS TRACHEITIS[1]

Case Report

WALTER I. WERNER

The literature of the past six years has been replete (Eloesser, Ballon, Samson, Barnwell, Burghes, Werner, Warren, Hammond and others) with descriptions of the symptomatology, bronchoscopic and pathological findings of tuberculosis of the trachea and the bronchi.

When this complication develops, symptoms and signs may be observed, which cannot be satisfactorily explained by the results of physical examination. With the more general acceptance of collapse therapy in the treatment of pulmonary tuberculosis, it is important that patients be bronchoscoped who give a history of or have the following obscure symptoms: (*1*) paroxysms of inspiratory or expiratory wheezing with or without sputum; the sputum may vary in character from white mucus to blood tinged with fibrin; (*2*) attacks of asthma or asthmatoid breathing; (*3*) large amounts of bacilliferous sputum with negative roentgenograms, or with only a small infiltration; (*4*) intermittent unexplained elevations of temperature, paroxysms of violent coughing, difficulty in raising sputum, dyspnoea and cyanosis. While bronchoscopy is not contraindicated in most cases of active pulmonary tuberculosis, it should be limited largely to those cases requiring special investigation.

The object of this paper is to report a case that was first treated for bronchial asthma, but was later diagnosed advanced pulmonary tuberculosis, and, while under artificial pneumothorax treatment, developed the above named symptoms.

L. T., a 35 year old, white married woman. Family history: father died of pulmonary tuberculosis. Past history is irrelevant. In 1932, she developed attacks of difficult breathing, wheezing and cough with mucoid sputum. A diagnosis of bronchial asthma was made. The patient's condition became slowly worse and, in March, 1936, tubercle bacilli were found in her sputum. Roentgenograms of the chest revealed an advanced fibrocaseous tuber-

[1] From the Maytag Laboratory of Southwestern Presbyterian Sanatorium, Albuquerque, New Mexico.

culosis of the left lung with cavitation. She came to Albuquerque and, in September, 1936, an artificial pneumothorax was induced on the left side. A good collapse of the lung was obtained, but there was considerable shifting of the mediastinum with herniation of the lung to the right. Because of this, small refills of air were given at two-week intervals, the closing pressure always being well on the negative side. The patient ran a very stormy course; she had fever, and developed an acute tuberculous laryngitis, also a pleural effusion. After six weeks, the fluid disappeared by resorption. The dyspnoea, which had been paroxysmal so far, became continuous. Her throat was always full of thick, tenacious sputum. She was pale and slightly cyanotic; her position in bed did not cause any change in the degree of dyspnoea. Inspiration was harsh, of a crowing, rasping quality. There was no impairment of the percussion note on the right side; bronchovesicular breathing and a few moderately coarse râles along the midscapular line were heard on auscultation. On the left side, the percussion note was high pitched, and the breath sounds were metallic in character. These signs and symptoms gave the clinical impression of tuberculous tracheitis with possible obstruction above the bifurcation. The patient's condition grew rapidly worse. There was an almost constant outpouring of foul-smelling, purulent sputum towards the end, and she expired January 22, 1937.

The first bronchoscopy was done on January 5, 1937, at which time the vocal cords on both sides were found thickened and markedly inflamed. The trachea was filled with a mass of granulation tissue, thought to be tuberculous. This granulation extended along the entire right main bronchus. Bronchoscopic examination was repeated three days later. The apparent granulations of the trachea then were explained as due to destruction of the cartilage. Forty-eight hours before death bronchoscopic examination revealed that the trachea had taken on a funnel shape, the mucosa appeared thickened, reddened, very oedematous and it was covered with ulcerated, white, cheesy areas which bled easily.

Postmortem examination: After removing the breast plate, the left lung was compressed about 50 to 70 per cent with numerous adhesions over the upper lobe, covering the anterolateral surface and extending to the first rib, and toward the apex. These adhesions varied in size from a fine string to the thickness of 1 cm. in diameter. Many adhesions were found over the posterior surface of the right upper lobe. The tongue, trachea, lungs and the heart were removed in one mass. The left aryepiglottic fold of the larynx was completely destroyed. The oesophagus appeared normal. The trachea felt firm, and there was no evidence of destruction of the tracheal cartilages. On opening, the trachea, starting at the level of the larynx and extending down to the bifurcation, showed marked ulceration with granulation along the posterior and posterolateral walls. The mucosa of both main bronchi was moderately

inflamed, but appeared otherwise normal. The left bronchus led to a thick-walled apical cavity, which measured 5 x 4 cm. Tuberculous acinous-nodose nodules were scattered throughout the left lung and were also noted in the base of the right upper lobe. The heart was negative. At no point in the tracheobronchial tree was there any evidence of stenosis or obstruction.

DISCUSSION

Tuberculous infection of the trachea, bronchi and of the bronchioli is a common occurrence in almost all tuberculous processes of the lung. In dealing with tracheal and bronchial obstruction, the question of asthma must always be considered in the diagnosis, for, at sometime or other, the diagnosis of asthma has been made in almost all cases in which patients have suffered from obstructive lesions of the respiratory tract, particularly if the obstruction has been associated with stridor. In the case reported, sudden attacks of coughing and wheezing, considered asthma, had occurred for four years, before the diagnosis of pulmonary tuberculosis, based on X-ray findings and sputum examination (1936), was made. The patient was always conscious of irritation and a feeling of fulness in her throat, with final symptoms of cyanosis and suffocation.

This condition apparently developed secondarily to the tuberculous parenchymal lesion. The efferent channels were continuously bathed with bacilliferous sputum and finally became infected. The tracheal lumen may be markedly reduced without causing alarming symptoms or killing the patient. In this compensated stage of breathing, respirations are slow, inspiration is much prolonged and expiration is unchanged, and mild dyspnoea is present only on exertion. The progress of the infection of the trachea was at first slow, which explains the gradual development of symptoms. At the height of this ulcerative process, however, dyspnoea became extreme and the respiratory stridor very marked. When partial stasis of the thick tenacious sputum occurred, the latter contributed much to the occlusion of the trachea, and this in turn interfered with the bronchial drainage, permitting development of anaerobic infection. The patient then became very toxic, had high fever, and she expelled foul-smelling, purulent sputum, copious in amount. She died with typical respiratory symptoms.

Only recent advances in X-ray and bronchoscopy, and the coöperation of the internist, bronchoscopist and roentgenologist have led to the clinical recognition of tuberculous tracheobronchitis as a clinical entity. Lesions of the tracheobronchial tree are exudative, caseous or pro-

liferative and probably cause clinical symptoms in from 10 to 15 per cent of all tuberculous patients. The occurrence of foul-smelling sputum is of great significance, as it indicates obstruction of the air passages. It appears early in lesions low in the tracheobronchial tree, and late, when the obstruction is located at its higher levels. As the prognosis of ulcerative tuberculous tracheobronchitis is always poor, thoracoplasty and other forms of major collapse therapy have no favorable effect.

SUMMARY

A case of pulmonary tuberculosis under artificial pneumothorax treatment, that developed asthmatoid wheezing and other signs of tracheobronchial obstruction, is reported, and the bronchoscopic and postmortem findings are described.

The author is indebted to Dr. Leroy S. Peters for permission to study this case, and to Dr. G. B. Ferguson for the bronchoscopic data.

REFERENCES

(1) Eloesser, L.: Bronchial stenosis in pulmonary tuberculosis, Am. Rev. Tuberc., 1934, *25*, 123.

(2) Ballon, D.: Bronchoscopy in the diagnosis of asthma complicating pulmonary tuberculosis, Ibid., 1935, *5*, 103.

(3) Samson, P. C.: Tuberculous tracheobronchitis, Ibid., 1936, *34*, 671.

(4) Burghes, J., Littig, J., and Culp, J.: Tuberculous tracheobronchitis, Its pathogenesis, Am. J. M. Sc., 1937, *193*, 515.

(5) Barnwell, J. B., Littig, J., and Culp, J. E.: Ulcerative tuberculous tracheobronchitis, Ibid., 1937, *36*, 8.

(6) Werner, W. I.: Bronchial obstruction as a complication of pulmonary tuberculosis under artificial pneumothorax, Am. Rev. Tuberc., 1935, *31*, 44.

(7) Warren, W., Hammond, A. E., and Tuttle, W. M.: The diagnosis and treatment of tuberculous tracheobronchitis, Ibid., 1938, *37*, 315.

SERIAL LEUCOCYTE COUNTS[1,2]

Their Practical Value in the Management of Pulmonary Tuberculosis

BENJAMIN J. ELWOOD AND THOMAS DE CECIO

There is no blood picture which distinguishes pulmonary tuberculosis from other infections; but once the diagnosis has been made by other means, the pattern of the peripherally circulating leucocytes is said to reflect accurately the nature of the pathological process (8, 12, 18, 19). Furthermore, serial determinations are reported to yield valuable indices of host resistance (2, 16, 21, 23, 24), to aid in the selection of therapy (3, 13, 20, 22) and gauge the latter's effectiveness (6, 10, 17, 20) and finally to develop a better estimate of prognosis (9, 10, 11, 12, 23). The simple laboratory procedure of blood counts would seem to assume an important place beside such a clinical aid as the radiograph, and perhaps be equally indispensable to proper management. Its enthusiastic endorsement by a number of investigators appears to leave no doubt concerning its value as a laboratory adjunct; and the addition of another paper to the voluminous literature already at hand would seem superfluous, unless one is able to contribute materially to the subject. Our own investigation is presented because our results and conclusions support the seldom reported but not uncommon opinion of the clinical inadequacy and not infrequent fallibility of the white blood cell picture. Our study further apparently fills the need, pointed out by Medlar (18), of an extended clinical and roentgenological interpretation and follow-up which is necessary for comparing the validity of the pathological concept developed from the leucocytic picture.

The course in the hospital of 206 consecutively admitted patients with pulmonary tuberculosis was managed without reference to or reliance upon any information gained from leucocyte counts. The latter examinations were made independently on over 1,800 occasions for future correlation. In all cases detailed analyses of serial changes were made

[1] Presented before the Clinical Section of the New Jersey Tuberculosis League, January 5, 1938.

[2] From the Hudson County Tuberculosis Hospital, Dr. B. S. Pollak, Medical Director, Jersey City, New Jersey.

during the period of hospitalization at least every month, at the time of any clinical complication and during the changes of pathological trends which were detected by fluoroscopy and radiographs. In this manner, changes in the accompanying leucocytic formulae could be traced for the development of possibly new interpretations and also be used to test the validity of pathological concepts established by others. Finally, separate prognoses, derived independently on the one hand from leucocyte counts and on the other from clinico-roentgenological observations, were drawn in 179 cases. The accuracy of each prediction could then be determined after a period of one to five years of careful observation. The whole investigation, therefore, represents an attempt to establish the practical application of the leucocytic blood picture to an otherwise complete and meticulous clinical study. The pathological standards of leucocytic variations and interpretation were utilized as advanced in the literature and bear no detailed repetition. The basic experimental concept that the picture of the leucocytes is a mirror of the pathological process and faithfully reflects the tissue changes going on is not disputed. The difficulty in evaluating the pathological state in human tuberculosis is also immediately recognized when a multiplicity of anatomical trends are simultaneously in evidence.

An analysis was first made of the initial leucocytic formula with a view to determine any possible specific value of the blood count routinely performed on admission. That the expression of nothing more than the trend of a previously undetermined blood picture would be reflected was borne in mind. Classification of the tuberculosis was made on a clinical and roentgenological basis into what proved the more meaningful types, listed in table 1.

The blood picture analysis disclosed that the lymphocytes and monocytes did not reflect significant developments, while a trend of a neutrophilic leucocytosis was indicative of the exudative process and a normal count for the productive lesion. The addition of cavitation to infiltrative lesions increased only the absolute levels without disturbing the relative proportions of the cells. The neutrophiles and total white count, when elevated, appear significant of an exudative or cavernous lesion or both. The application of this additional knowledge to the initial clinical evaluation of a case conceivably merits consideration and perhaps more intimate study. Otherwise, the findings tend to bear out the observation that healed or healing forms of pulmonary tuberculosis yield a leucocytic picture not at great variance, if at all, with the normal.

The analysis of serial alterations in the leucocytic formula during the known development of specific pulmonary changes was then attempted. Seven hundred and seventy-two instances of various anatomical trends documented by serial X-ray films were accumulated during the period of hospitalization. Only thus could such extraneous factors as menstruation, haemoptysis, diarrhoea, emesis or physical activity be excluded as possibly influencing the blood picture. The extent of the influence of occultly active extrapulmonary processes on the leucocytic reaction cannot be evaluated adequately and therefore has not been considered. It is interesting to note that, at some time or other during the blood study, extrapulmonary lesions reached a clinically recognizable stage in 60 of 200 cases for a total confirmed involvement of 84 organs or systems. This relatively large incidence of such additional disease

TABLE 1

Analysis of the initial leucocytic formula

INITIAL PATHOLOGY	TOTAL WHITE COUNT		NEUTROPHILES		LYMPHOCYTES		MONOCYTES	
	Average count	Per cent within normal range	Average count	Per cent within normal range	Average count	Per cent within normal count	Average count	Per cent within normal range
Exudative....	10,500	33	7,100	0	2,900	100	630	33
Productive....	8,700	78	5,800	22	2,300	67	400	89
Exudative cavernous...	11,700	32	7,550	13	2,730	92	700	74
Productive cavernous...	9,200	55	6,200	30	2,600	88	410	91

probably can be duplicated in any program with repeated objective examinations of the extrapulmonary systems. The additional effect upon the blood picture of specific therapeutic measures, such as pneumothorax or thoracoplasty, was not determined because, first, they are largely mechanical measures and, second, only resultant pathological changes are given primary consideration. In retrogressive trends of pulmonary lesions, such as resorption, fibrosis, absence of progression and decrease or closure of cavitation, significant haematological variations could not be observed. With the occurrence of progressive phases of disease such as spread, development of or increase in cavitation and effusion (empyema?), no significant changes were noted when the previous haematological levels were elevated; but when the preceding levels were normal a tendency to elevation was noted in the total and neutrophilic

counts. An example is shown in table 2. This represents a significant quantitative alteration which lends itself for interpretation in a limited and variable number of instances, conditioned by the presence of a previously normal haemogram. A continuation of such known leucocytic increases may then be respected as a similar qualitative finding. Clinically applied, the development or continued presence of a neutrophilic leucocytosis should portend or confirm the more immediate existence of some form of progression of the disease. Even if one grants the applied value of this concept, the careful clinical routine adopted

TABLE 2

Analysis of alterations in leucocytic formulae at the time of specific pathological changes

Example—Spread

PREVIOUS LEVEL	NUMBER	CHANGE			FINAL LEVEL	
		Dropped	No change	Elevated	Normal	Elevated
Total						
Normal	*45*	2	2	41	*13*	*32*
Elevated	109	48	2	59	19	90
Totals	154	50	4	100	32	122
Neutrophiles						
Normal	*21*	1	0	20	*3*	*18*
Elevated	133	55	1	77	5	128
Totals	154	56	1	97	8	146
Monocytes						
Normal	87	18	3	66	53	34
Elevated	67	37	1	29	17	50
Totals	154	55	4	95	70	84
Lymphocytes						Subnormal
Normal	125	75	3	47	100	25
Subnormal	29	1	0	28	19	10
Totals	154	76	3	75	119	35

disclosed not only the pathological trend but also the specific anatomical change.

Studies of the rôle of the various leucocytes have led to the description of more detailed formulae alterations (1, 4, 5, 7, 14, 15, 16, 25, 26, 27), which for clinical purposes should indicate the course of underlying pathological changes. Both the alteration and the interpretation given the various formulae were accepted in an attempt to test their validity in a given series of well documented pathological trends. Where serial leucocytic pictures were so applied, the alterations of the formulae con-

curred with accepted standards in 61 per cent of several hundred instances of known pathological changes. The remaining 39 per cent were of no significance or contradictory (table 3).

Adequate clinical conformity is noted however in such individual pathological changes as spread, development of or increase in cavitation, and effusion, averaging approximately 80 per cent for each. On the other hand, pathological agreement is seen in no more than 30 to 50 per cent of instances of regressive trends of pulmonary disease. Although figures of 30 to 50 per cent may represent significant values from an

TABLE 3

Frequency of compliance of alterations in leucocytic formulae with accepted standards for various pathological trends

ALTERATION IN LEUCOCYTIC FORMULA	PATHOLOGICAL CHANGE							TOTALS
	Resorption	Spread	Cavitation			No change	Effusion	
			Present or increased	Decreased	Closed			
Typical ..	15	88	57	4	1	61	11	237
Some significance ..	19	34	24	13	7	101	9	207
Total ..	34(38%)	122(80%)	81(80%)	17(50%)	8(30%)	162(53%)	20(77%)	444(61%)
No significance ..	24	14	12	8	7	77	5	147
Contradictory	28	16	11	9	12	66	1	143
Total ..	52(62%)	30(20%)	23(20%)	17(50%)	19(70%)	143(47%)	6(23%)	290(39%)
Total	86	152	104	34	27	305	26	734

experimental point of view, a greater frequency of appearance is necessary for clinical application. Even if the more or less limited knowledge derived from the interpretation of the leucocytic alterations had been applied in the clinical management of these cases, it appears that not a few instances of progressing lesions would not have been apprehended as early, and a varying majority of examples of apparently retrogressing disease would have belied the encouragement expressed in the clinical estimate. The attempts further to place into practice the various interpretations of correlated blood picture changes, whether detailed or

restricted in scope, may be stated to reward the clinician only in the narrow field of progressive pulmonary disease.

The study of the applied value of leucocytic formulae in the problem of prognosis is probably the most interesting phase of the investigation and entails an unbroken continuity of clinical and roentgenological observation for a period as long as five years, not less than one year, and an average of three years in the vast majority of instances. It should be added, however, that alterations of the pathological states after three years were too few to influence statistics materially. At the completion of blood studies then, which for 179 cases (table 4) occurred either at discharge or release, or at an arbitrarily fixed time for those still confined, two prognoses were estimated for each individual, one based upon the correlation of clinical and roentgenological findings, and the other fashioned from the trend of the blood picture. Despite the regard for subsequent well-being, good capacity for work, or maintained clinical stability, any case exhibiting unequivocal anatomical progression was considered as having fared unfavorably. Such a severe and strictly anatomical criterion is not noted elsewhere in the literature which more often reveals an evaluation based on the evidence of the clinical state.

Accordingly, 69 patients, almost exclusively with favorably solved therapeutic problems, were discharged from the sanatorium. Their prognoses based on the clinical estimate proved correct in 55 instances or approximately 80 per cent, whereas when judged on the basis of a leucocytic picture their courses were substantiated in only 17 instances or approximately 25 per cent.

A not less critical analysis may be made of 51 persons released from the hospital against advice. This group may serve as an intermediate control and distinctly favors opportunities for substantiation of the prognosis based on the leucocytic picture, as releases occurred at a time considered clinically premature for many and definitely unrecommended for the remainder. From a therapeutic standpoint the group represents individuals with incompletely or recently solved disease problems. The clinico-pathological estimate of prognosis nevertheless was borne out in 72.5 per cent, and the prognosis gained from study of leucocytic formulae was confirmed in 58.8 per cent. The drop in degree of accuracy of clinical prediction in this group may be well attributed to the hazards of prognostication in those instances in which the patient forces the more impractical conditions for continuation of treatment or observation. The increase in accuracy of the leucocytic estimate may be developed below.

The remainder of the cases comprised a group whose residence in the hospital had been advised and continued, obviously because of uncontrolled or progressive disease, and at the time of completion of the present

TABLE 4

Comparative prognostic value of the leucocytic picture and a clinico-pathological estimate

GROUP	PROGNOSIS		NUMBER	SUBSEQUENT COURSE		PREDICTED CORRECTLY	
				Favorable	Unfavorable	Number	Per cent
Discharged with consent	Clinical	Favorable	68	55	13	55	
		Unfavorable	1	1	0	0	
			69	56	13	55	79.8
	Leucocytic	Favorable	18	11	7	11	
		Unfavorable	51	45	6	6	
			69	56	13	17	24.6
Released against advice	Clinical	Favorable	25	14	11	14	
		Unfavorable	26	3	23	23	
			51	17	34	37	72.5
	Leucocytic	Favorable	10	3	7	3	
		Unfavorable	41	14	27	27	
			51	17	34	30	58.8
Hospitalization continued	Clinical	Favorable	17	11	6	11	
		Unfavorable	42	2	40	40	
			59	13	46	51	86.4
	Leucocytic	Favorable	0	0	0	0	
		Unfavorable	59	13	46	46	
			59	13	46	46	77.9
Summary	Clinical	Favorable	110	80	30	80	72.7
		Unfavorable	69	6	63	63	90.0
			179	86	93	143	79.8
	Leucocytic	Favorable	28	14	14	14	50.0
		Unfavorable	151	72	79	79	52.0
			179	86	93	93	51.9

study was evaluated as to ultimate prognosis. The prediction of an unfavorable pathological course should characterize the majority of the clinical estimates, and if a true value has been attached to our concept of the interpretability of the blood picture the leucocytic formula should

return its greatest accuracy in this group. Precisely the clinical impression has been borne out in 51 of 59 instances (86.4 per cent) and the leucocytic evaluation has been confirmed in 46 (77.9 per cent). The opportunity for clinical application of the leucocytic picture apparently increased proportionately as the type of disease is encountered in a progressive form. This is shown consistently in every phase of the investigation.

Utilizing the summary in table 4, the gross accuracy of each method for predicting favorable or unfavorable prognosis may be determined so that a representative value may be attached for clinical application. It may be noted then that, where clinical restrictions are removed from the estimate, the leucocytic impression fails, for all intents and purposes, as often as it succeeds. On the other hand the degree of confirmation of the clinical impression is high for unfavorable prediction, and satisfactory when a favorable estimate is made.

SUMMARY AND CONCLUSIONS

A study of leucocytic formulae was made with a view to establish their limits of practicability in an otherwise careful management of pulmonary tuberculosis. It was found that:

1. The evaluation of the initial leucocytic formula discloses that the neutrophilic and total leucocytic levels are significant when elevated of an exudative or cavernous lesion or both. The lymphocytic and monocytic levels and proportions are not significant for clinical interpretation. The application of this knowledge to the initial clinical estimation of tuberculosis conceivably merits consideration.

2. An analysis was made of the clinically significant alterations in the leucocytic formulae during the known course of specific pathological changes. In instances indicating regressive anatomical trends, no clinically interpretable changes in the leucocytic formula could be found. With the occurrence of progression of disease, as indicated by spread, excavation or formation of effusion (empyema?), a significant tendency toward the development or maintenance of a neutrophilic leucocytosis was observed. Differential characteristics for the specific nature or form in which disease advances or activity takes place could not be established. A careful correlation of clinical and roentgenological findings disclosed instances in which the intrinsic value of the blood picture might have asserted itself. Nevertheless a pathological concept may be drawn which for immediate clinical purposes is limited to the recognition

of a simple trend in the blood picture to portend or confirm activity or advancement of disease.

3. A wide test of the validity of a more detailed concept of the significance of leucocytic changes found a concurrence with established standards in 61 per cent of several hundred instances of pathological changes. When individual anatomical trends were considered a more significant and clinically applicable incidence of compliance of blood counts was noted with the occurrence of such progressive phases as spread, cavitation or effusion. On the contrary, contradictory or non-significant formulae were largely noted in the various expressions of retrogressing lesions. Attempts to find a yield of significant compliance in more detailed pathological trends were even less successful. The broad application of concepts advanced for the interpretation of leucocyte counts, however scientifically sound, finds insufficient clinical correlation.

4. Accuracy of the clinico-roentgenological estimate of prognosis occurs in an impressive majority and exceeds significantly that based on serial leucocyte counts. The results of application to prognosis bear out consistently the limitation of the blood picture interpretation of advancing pulmonary tuberculosis.

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REFERENCES

(1) Bender, L., and De Witt, L. M.: Am. Rev. Tuberc., 1923, *8*, 138.
(2) Boissevain, C. H., Forster, A. M., and Good, B. D.: Ibid., 1936, *34*, 477.
(3) Brock, B. L.: Ibid., 1930, *21*, 745.
(4) Camp, W., Lutton, F. H., Tompkins, E. H., and Cunningham, R. S.: Ibid., 1928, *18*, 462.
(5) Cunningham, R. S., Sabin, F. R., Sugiyama, S., and Kindwall, J. A.: Bull. Johns Hopkins Hosp., 1925, *37*, 231.
(6) Deegan, J. K.: Am. Rev. Tuberc., 1933, *30*, 256.
(7) Doan, C. A., and Sabin, F. R.: J. Exper. Med., Supplement 3, 1930, *52*, 113, 138.
(8) Finner, L. L.: Am. Rev. Tuberc., 1930, *21*, 764.
(9) Flinn, J. W., and Flinn, R. S.: Ibid., 1929, *20*, 347.
(10) Flinn, J. W., Flinn, R. S., and Flinn, Z. M.: Ibid., 1933, *27*, 488.
(11) Griesbach, R.: Ztschr. f. Tuberk., 1930, *56*, 177.
(12) Kaminsky, J.: New England J. Med., 1934, *211*, 245.
(13) Kaminsky, J.: Am. Rev. Tuberc., 1935, *31*, 480.
(14) McJunkin, F. A.: J. Med. Res., 1920, *42*, 201.
(15) Medlar, E. M.: Am. J. Path., 1926, *2*, 275.
(16) Medlar, E. M.: Am. Rev. Tuberc., 1929, *20*, 312.
(17) Medlar, E. M.: Ibid., 1935, *31*, 628.

(18) MEDLAR, E. M.: Ibid., 1935, *31*, 642.
(19) MEDLAR, E. M., AND KASTLIN, G. J.: Ibid., 1927, *16*, 706.
(20) MEDLAR, E. M., AND PESQUARA, G. S.: Ibid., 1931, *23*, 367.
(21) MORRIS, W. H., AND TAN, S. H.: Ibid., 1927, *16*, 729.
(22) MULLER, G. L.: Ibid., 1937, *35*, 83.
(23) MULLER, G. L.: New England J. Med., 1934, *211*, 248.
(24) OATWAY, W. H., JR.: Am. Rev. Tuberc., 1934, *29*, 73.
(25) SMITHBURN, K. C., SABIN, F. R., AND HUMMEL, L. E.: Ibid., 1937, *36*, 673.
(26) WHITE, W. C.: Arch. Path. & Lab. Med., 1927, *3*, 84.
(27) WRIGHT, B. L., AND KING, R. W.: Am. J. M. Sc., 1911, *141*, 852.

OLIVE OIL IN PNEUMOTHORAX[1]

Its Influence on the Development and Course of Pleural Fluids during the Course of Artificial Pneumothorax

SPENCER SCHWARTZ AND FRED H. HEISE

It has been reported that the injection of a small amount of sterile olive oil into the pleural cavity soon after the induction of artificial pneumothorax helped to prevent the development of pleurisy with effusion later on during the course of pneumothorax treatment (2).

From April 1, 1933 until the spring of 1937, almost all of the patients in whom pneumothorax was induced at the Trudeau Sanatorium had from 2 to 4 cc. of sterile olive oil injected intrapleurally at the end of the second or third refill. The immediate reaction, if any, consisted of moderate to severe pain in the chest in about one-half, and fever from 99.1° to 100°F. (rarely higher) in about one-fourth of the cases. This reaction, when present, lasted one or two days and was never of any serious consequence.

All patients receiving pneumothorax that were discharged during the years from 1933 to 1937 inclusive were studied. Thus, other pneumothorax patients who were at the Sanatorium, but who did not receive oil, served as controls. In most of these, pneumothorax had been started previous to admission. Some were started at the Sanatorium before oil was used and a few were spared because the patient or the physician feared the attendant pain in the chest. Both of these groups were followed for from one to four years after discharge.

Pneumothoraces consisting of only a small pocket, which were soon abandoned, were not included in the study. Also, simultaneous bilateral cases were not included because they only added confusion to an already confusing problem.

Of a total of 285 cases, 139 received oil and 146 did not receive it. All these were analyzed with respect to: (*1*) the extent and type of lesion as seen in the X-ray film; (*2*) the size of the cavity; (*3*) the location of cavity or disease; (*4*) effectiveness of collapse; (*5*) presence of fever before, after, or during the time of induction of pneumothorax; and

[1] From the Trudeau Sanatorium, Trudeau, New York.

(*6*) presence of fever or pain after the injection of oil. An attempt was made to see what effect these factors had on the development of fluid.

The cases were also divided into three groups, depending on whether they developed no fluid, simple fluid or troublesome fluid. Simple fluids were considered to be those which develop asymptomatically and in small amounts, and which may or may not persist. Small transient fluids developing after internal pneumonolysis, accompanied by a little fever for a few days, also were included in this group. None required tapping. All fluids greater in amount or severity than the simple fluids were called troublesome fluids; in other words, those requiring tapping, those with an acute febrile onset, and those developing asymptomatically to an amount of several hundred cc.

The incidence of troublesome fluid was found to be influenced by the type of lesion as seen in the X-ray film before the beginning of pneumothorax. Troublesome fluid developed in 12 per cent of the patients whose lesions were regarded as inactive proliferative, in 17 per cent of those regarded as active proliferative, and in 29 per cent regarded as active exudative. The incidence of troublesome fluid was found to be increased in patients having fever after the injection of oil (33 per cent), as opposed to those not having fever at that time (17 per cent). Troublesome fluid developed in 32 per cent of patients having cavities larger that 3 cm. in diameter, whereas the general average was 25 per cent.

All other factors, that is, extent or location of the lesion, effectiveness of collapse (87 per cent were effective), pain after the injection of oil, and fever due to the tuberculous process at the time of induction of pneumothorax, had no effect upon the incidence of troublesome fluid.

Next, the effect of the injection of oil upon the incidence of troublesome fluid was considered. The two groups of patients were entirely comparable, that is, those receiving oil and those not receiving it, with the following exceptions:

1: The type of lesion as seen in the X-ray film before beginning pneumothorax. Of those receiving oil, 10 per cent were thought to be inactive proliferative, 50 per cent active proliferative and 40 per cent active exudative. Whereas of those not receiving it, 14 per cent were thought to be inactive proliferative, 23 per cent active proliferative and 63 per cent active exudate. However, the type of lesion was not known in about half of the latter group, so this difference may or may not be real.

2: Fever at the time of induction of pneumothorax was present in 42 per cent of those receiving oil, and in 55 per cent of those not receiving it. Since this

factor was found to have no influence upon the development of fluid, the difference is not important.

Of the 139 cases receiving oil, 37 per cent developed no fluid, 41 per cent simple fluid and 22 per cent troublesome fluid; while of the 146 cases not receiving it, 34 per cent developed no fluid, 39 per cent simple fluid and 27 per cent troublesome fluid.

When these patients' postdischarge records, extending over a period of from one to three years, were studied, it was found that 68 per cent of those who received oil were well and working and 6 per cent were dead; while 61 per cent of the control group were well and working and 12 per cent were dead. The present condition of less than 1 per cent was unknown. The rest had relapsed or had not yet returned to work.

In the patients receiving oil, 56 per cent of the simple fluids developed within the first month after beginning pneumothorax, and 76 per cent within three months; while in the control group 40 per cent developed within one month and 60 per cent within three months. Troublesome fluids developed later in both groups. In the oil cases, 6 per cent developed within one month and 39 per cent within three months; while in the nonoil group 13 per cent developed within one month, and 33 per cent within three months. However, most of both types of fluids developed within six months. By this time, 90 per cent of the simple and 68 per cent of the troublesome fluids had developed in the oil group, while in the control group 86 per cent of the simple and 77 per cent of the troublesome fluids developed within this period.

The beneficial effects of oil are more evident when the severity and course of the troublesome fluids are considered (table 1). Tubercle bacilli and pus were less frequent in the fluids of the oil group, more of the fluids disappeared spontaneously or with only a little treatment, and fewer persisted in spite of treatment. Also, while the same percentage of cases were well and working in both groups, less than one-half as many of the oil group were dead.

There were some other observations made in which the number of cases involved were insufficient to make it worth while to put them into tables.

In three instances, spontaneous pleurisy with effusion was converted into pneumothorax. In two the fluid disappeared after tapping the chest once or twice, the third after many tappings; replacement of the fluid with air being the only treatment used. The lungs of two of the

patients have since been expanded and all are well and working at present.

Oleothorax was used four times, either to provide increased compression of the lung or to prevent premature reëxpansion. Troublesome fluid was not present previously but developed afterward in all of the cases. In one the fluid disappeared after one or two tappings, and this patient is now well and working. One had a thoracoplasty but is still chronically ill. One is still chronically ill from the effects of persistent fluid, and one died of a tuberculous empyema.

Internal pneumonolysis was done in 45 cases, only 2 (4 per cent) were followed by troublesome fluid.

TABLE 1

Tapped troublesome fluids

	NUMBER OF CASES	TUBERCLE BACILLI				PUS	SECONDARY ORGANISMS
		Not known	None	Gaffky 1–3	Gaffky 3+		
		per cent	*per cent*	*per cent*	*per cent*	*per cent*	*per cent*
Oil	21	5	43	38	14	14	10
No oil	30	20	17	43	20	37	10

Troublesome fluids

	NUMBER OF CASES	DISAPPEARANCE			PERSISTING FOLLOWING MANY TAPS	WELL AND WORKING	DEAD
		Spontaneous	Following 1–2 taps	Following many taps			
		per cent	*per cent*	*per cent*	*per cent*	*per cent*	*per cent*
Oil	31	32	39	10	19	48	10
No oil	39	23	31	18	28	49	23

Local treatment, other than surgical measures, consisted of irrigations with normal salt solution or azochloramid, oleothorax, dyes when secondary organisms were present, and replacement of the fluid with air. Salt solution exerted a favorable effect toward bringing about the disappearance of fluid in 2 of 5 instances; azochloramid in 1 of 3; oleothorax in 3 of 7; dye removed secondary organisms in 1 of 2; and replacement with air sufficed in 26 of 35.

In order to have a study of pneumothorax cases extending over a longer period of time, the postdischarge records of a series of 157 cases previously reported by Heise and Paine were reviewed (1). These patients were discharged from the Sanatorium between 1929 and 1932, thus

permitting observation for a period of from five to eight years after discharge. None of them received oil (table 2).

Of these, 40 per cent developed no fluid, 49 per cent simple fluid and 11 per cent troublesome fluid during their stay at the Sanatorium. The lower incidence of troublesome fluid and the higher one of simple fluid in this series of cases as compared with the one just reported is probably due to lack of detailed knowledge as to the amount of fluid developed, and the symptoms of the patient during its development. This resulted in some of the milder troublesome fluids being placed in the simple fluid group. This explanation is made still more reasonable when it is noted that only three of the troublesome fluids in this series were not tapped.

Twenty-three of these cases who had been free from this complication during residence, developed troublesome fluid after discharge. Thus 25 per cent of this series of cases have developed, and by inference 40

TABLE 2

157 nonoil cases—observed five to eight years after discharge

	WELL AND WORKING	DEAD	LUNG RE-EXPANDED	LUNG NOT RE-EXPANDED	TROUBLESOME FLUID AFTER DISCHARGE
	per cent	*per cent*	*per cent*	*per cent*	*per cent*
No fluid	70	22	65	16	16
Simple fluid	82	12	66	21	17
Troublesome fluid	59	41	47	53	12

per cent of the more recent series will develop troublesome fluid before reëxpansion of the lung has taken place, or if pneumothorax is continued for five years or more.

Of the whole series of 157 patients, 75 per cent were well and working, 5 per cent relapsed or chronic, 19 per cent dead, and 1 per cent unknown. It may be seen (table 2) that the present condition of those who had troublesome fluid is worse, and that fewer have had their lungs re-expanded than in the other groups.

There were 30 patients who died. Of 14 who had no fluid during residence, 9 died of pulmonary tuberculosis, one of tuberculous empyema, and 4 of other causes. Of the 9 who had only simple fluid, 8 died of pulmonary tuberculosis and one of a nontuberculous illness. However, of the 7 who had troublesome fluid, only 2 died of pulmonary tuberculosis, 4 of tuberculous empyema, and one of a nontuberculous illness.

Even in the small numbers involved the influence of reëxpansion of the lung on the end results of troublesome fluid is striking. All 8 patients with reëxpanded lungs are now well and working, while 7 of the 9 with lungs remaining collapsed are now dead. Four of them died of tuberculous empyema. Undoubtedly, when troublesome fluid develops, reexpansion of the lung is advisable unless some strong contraindication is present.

SUMMARY

1. The type of lesion as seen in the X-ray film, the presence of large cavities and the presence of fever after the intrapleural administration of a small amount of olive oil influence the incidence of troublesome fluid.

2. The intrapleural instillation of a few cc. of sterile olive oil shortly after the induction of pneumothorax lowers the incidence of troublesome fluid slightly, and diminishes the severity of these fluids considerably.

3. From 25 to 40 per cent of patients receiving pneumothorax treatment develop troublesome fluid when followed until reëxpansion of their lungs has taken place, or if pneumothorax is continued for five years.

REFERENCES

(1) HEISE, F. H., AND PAINE, D.: Pleural fluids during artificial pneumothorax treatment in pulmonary tuberculosis, Tr. Am. Clin. & Clim. Assn., 1934.

(2) UNVERRICHT AND DOSQUET: Methode zur Vermeidung von Pneumothoraxexudaten, Deutsche med. Wchnschr., 1933, *59*, 451.

TUBERCULIN SURVEY[1]

Observations on Medical Students and Undergraduate Nurses at Vanderbilt University

A. E. KELLER AND R. H. KAMPMEIER

Among the various activities now emphasized by the Student Health Service is the early detection of pulmonary tuberculosis. The importance of this is twofold. First, pulmonary tuberculosis is a disease taking its toll in early adult life and should therefore be diagnosed as early as possible to insure the best chance of cure. Second, because of intimate contacts among students, early detection of pulmonary tuberculosis is of great importance as a preventive measure.

In 1932 the American Student Health Association created a Committee to study tuberculosis in student groups to the end of encouraging a more aggressive, effective approach to the problem. In 1935 Shepard (1) presented some of the findings of this Committee.

About ten years ago, studies were begun at several schools of nursing and medicine relative to the acquisition of positive tuberculin reactions by students during their period of training. This phase of student health activity received its main impetus from Heimbeck's (2) work in Norway. In this country, such studies have been carried out by Geer (3), Hetherington and associates (4, 5), Herman, Baetjer and Doull (6), and Long and Seibert (7).

Little has been published relative to the incidence of tuberculosis or tuberculous infection in students of southern colleges or universities. In the American Student Health Association report (1) figures are included from two southern schools. Agnes Scott College in Georgia reported one case of tuberculosis, an incidence of 0.22 per cent and positive tuberculin tests in 18 per cent of the student body. At Clemson College in North Carolina, 35 per cent of those tested were found to be positive to tuberculin, and 0.37 per cent presented evidence of pulmonary tuberculosis. Long and Seibert (7) record that 48.3 per cent of 120 Emory University medical students gave positive reactions when tested with Purified Protein Derivative.

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Since data from the south are meagre, it is felt that our studies among students of medicine and nursing at Vanderbilt University should be of interest and value in extending knowledge of the incidence of tuberculous infection among college students.

MATERIAL AND METHOD

Students in the Vanderbilt University School of Nursing from 1931 to 1936 and students in the Vanderbilt University School of Medicine from 1929 to 1937 comprise the material for this study. Of the medical students, 90 per cent were males. The average age of the medical students on admission was twenty-two years and of the nurses twenty-one years.

The tuberculin tests were made with Old Tuberculin, using the Mantoux method. During the first years the minimal dose of tuberculin used was 0.1 mg. and those negative to this were retested with 1.0 mg. As the result of several unfavorable reactions with this initial dose, we adopted in 1932 0.01 mg. as the dose for the first test. Nonreactors were then retested with 0.1 mg. and finally with 1.0 mg. Tests were interpreted by two observers forty-eight hours after the injection. No student was classified as tuberculin-negative unless 1.0 mg. of Old Tuberculin failed to induce the reaction. Those students who gave positive reactions at the first testing were not retested until their last year in school. Students with negative reactions were retested each succeeding year.[2]

RESULTS

During the 1929–1937 period, 555 medical students were tested on admission. Of that number, 220, or 40 per cent, gave negative reactions to all quantities of tuberculin and 335, or 60 per cent, had positive reactions to one of the three doses. In this period of observation the highest incidence of tuberculous infection, as indicated by positive reactions, was 81.1 per cent, and occurred in 1931, and the lowest incidence, 31.5 per cent, in 1937.

In the group of 198 student nurses tested during the period 1931–1936, 91, or 46 per cent, were found to have negative tuberculin tests with the three doses of Old Tuberculin and 107, or 54 per cent, were found to be

[2] This study was initiated by Doctors Horton Casparis and Katherine Dodd of the Department of Pediatrics, Vanderbilt University School of Medicine. The data for the early years of this study were compiled by them.

positive to one of the three quantities used. The highest incidence of tuberculous infection, 74 per cent, occurred in this group in 1931 and the lowest incidence, 27 per cent, in 1936. Table 1 shows these data.

Four hundred forty-three, or 80 per cent, of the medical students resided in the southern states and attended college in this area before entering medical school. The remaining 112 came from twenty-one other states, in which all parts of the country are represented. As regards the student nurses for whom data as to residence are available, 90 per cent came from southern states and a majority from Tennessee and contiguous areas.

It was found that there was approximately as great an incidence of tuberculous infection in students who had resided in rural areas as in students coming from urban communities.

TABLE 1

Results of tuberculin tests on students in the Schools of Medicine and Nursing of Vanderbilt University

GROUP	NUMBER TESTED	NEGATIVE		POSITIVE*	
		Number	Per cent	Number	Per cent
Medical students	555	220	40.0	335	60.0
Undergraduate nurses	198	91	46.0	107	54.0
Total	753	311	41.4	442	58.6

* Positive tests indicate that the students reacted typically to either 0.01 mg., 0.1 mg., or 1.0 mg. of Old Tuberculin. Only the first tuberculin test on each medical student and nurse, performed on admission to their respective schools, is included in the table.

Long and Seibert (7) reported the incidence of positive tests with Purified Protein Derivative in students entering colleges in various sections of the United States in 1935 and 1936. Since our students were tested on admission to the Schools of Medicine and Nursing of Vanderbilt University, before "professional exposure" to infection had occurred, the results obtained may be used as a means of comparing the incidence of tuberculous infection in southern college students with that found in other parts of the country.

For college students in the eastern section of the United States the average incidence of tuberculous infection was 49.7 per cent; in the middle west 26.7 per cent; in the far west 44.6 per cent. For our group of students the incidence of infection was 58.6 per cent. Long and Seibert (7) believe the difference in incidence of positive tuberculin

tests in eastern and midwestern sections is related to the density of the population in the former as compared with the latter. In the case of the far west they consider that immigration of patients with tuberculosis has been at least partly responsible for the spread of the disease and for maintaining a high rate of tuberculous infection. In the southern area the average uncorrected mortality per 100,000 population for all forms of tuberculosis, according to Lumsden and Dauer (8), was 81.7 for the period 1929–1933. The corresponding mortality rates for the eastern, the middle west and the far west were respectively 59.3, 47.9 and 94.4. It would seem that in the relatively sparsely populated southern area the large amount of tuberculosis in the general population, as indicated by the high mortality rate, is responsible for the high incidence of tuberculous infection we have encountered in students.

TABLE 2

Number of students developing positive tuberculin reactions while in medical or nursing school

YEAR OF "EXPOSURE"	MEDICAL STUDENTS			STUDENT NURSES		
	Number tested	Number positive	Per cent positive	Number tested	Number positive	Per cent positive
First.....	123	16	13.0	54	4	7.4
Second.....	116	15	12.9	23	4	17.4
Third.....	87	20	22.9			

It is of interest to determine how many students develop positive tuberculin tests during their medical and nursing courses and also to find out during what years they are most likely to develop evidence of sensitization to tuberculoprotein. All students who had negative tests on admission and for whom one or more negative observations have been recorded were studied.

In interpreting the data in table 2, it should be remembered that while the medical students were tested once a year during the four years, the tests were performed at the beginning of each school year. This means that the tuberculin reactions obtained on admission should be interpreted with relation to the preceding years and those found in the second, third and fourth years with relation to "exposure" during the first, second and third years in the medical school. The term "exposure," as used, indicates the casual contact that a medical student would meet in his routine activities. Student nurses were tested once a year for three years, and as in the case of medical students the tests during their

second and third years represent respectively one and two years of exposure.

Of the medical students represented in table 2, 15 per cent were students who entered the Vanderbilt University School of Medicine following the completion of their second year in some other southern institution. We have included the "transfers" with our own students because we believe that the exposure to tuberculosis during their preclinical years was no greater than that experienced by our own students.

The increase in the percentage of positive reactors in the third year of "exposure," shown in table 2, may be accounted for in all probability by the fact that this represents the students' first year in clinical medicine.

With regard to student nurses, table 2 shows essentially the same facts in that 17.4 per cent of 23 nurses who had had negative tests developed positive tuberculin tests following their second year of "exposure." The second year of "exposure" represents the student nurse's first year of intensive ward work.

It is of interest to note that of the 51 medical students who developed positive tests following "exposure" as indicated in table 2, 16 gave a positive test with 0.01 mg., 10 with 0.1 mg., and 25 with 1.0 mg. of Old Tuberculin.

Of the 8 student nurses who developed positive tuberculin tests following "exposure," 5 gave positive reactions with 0.01 mg., one with 0.1 mg., and 2 with 1.0 mg. of Old Tuberculin.

Among the 555 medical students, 51 developed a positive tuberculin reaction during their medical course. If this number is related to the number with positive tests on admission to the school it will be seen that during the school period the total incidence of tuberculous infection increased from 60 to 69.5 per cent. Among 198 student nurses, 8 developed a positive reaction during their training period. Thus in this group the incidence of tuberculous infection increased from 54 to 58 per cent.

Our experience in this respect is similar to that of Hetherington, McPhedran, Landis and Opie (5).

An interesting observation was made with regard to students who gave positive tuberculin reactions on admission to the school and who were retested during the fourth year. Table 3 shows that of 84 students who were positive reactors in the first year, 11 had become negative to all three quantities of tuberculin in the fourth year. Of 7 students

positive in the second year, 4 had become negative when retested in the fourth year and of 11 students positive in the third year, 6 had become negative in the fourth year. To summarize the data it may be said that of 102 students who originally gave positive tuberculin tests, 21, or 20.5 per cent, gave negative tests to as much as 1.0 mg. of Old Tuberculin from one to three years later. It should be stated that these data do not include all students who had positive tests on admission but only those whom we were able to retest in the fourth year.

Our records were reviewed to determine the amount of tuberculin to which the 21 negative reactors in table 3 had given positive tests originally. It was found that 5 of the 21 had given positive reactions to 0.1 mg. of Old Tuberculin and the remaining 16 gave positive reactions only when 1.0 mg. of Old Tuberculin was used.

TABLE 3

The development of negative tuberculin reactions in medical students and student nurses who originally gave positive reactions

GROUP	INITIAL TEST POSITIVE	SUBSEQUENT TESTS	
		Positive	Negative
Medical Students:			
Group A, positive first year, retest fourth year	84	73	11
Group B, positive second year, retest fourth year	7	3	4
Group C, positive third year, retest fourth year	11	5	6
Total	102	81	21
Student Nurses:			
Group A, positive first year, retest second year	37	28	9

As in the case of medical students, observations were made on 37 nurses who exhibited positive tuberculin reactions on admission and who were retested one year later. Of the 37 nurses with positive tuberculin tests, 9, or 24.3 per cent, were negative to all three doses of tuberculin one year later. Of these 9 students whose tests became negative, 3 originally were positive to 0.1 mg. and negative to 0.01 mg. of Old Tuberculin and 6 were originally positive to 1.0 mg. and negative to 0.1 mg. of Old Tuberculin.

DISCUSSION

In the study carried out in the Vanderbilt University Schools of Medicine and Nursing, tuberculin tests were done upon admission to these

schools. Thus the reactions in these students represent the incidence of tuberculous infection in a college group before the possibility of increased exposure to the disease had taken place in the medical school or hospital. As such, this group of southern students shows a higher incidence of tuberculous infection than occurred in colleges of the eastern, midwestern and far-western sections of the country, as reported by Long and Seibert (7).

It should be noted that the average age of the medical students was twenty-two years, and of the nurses twenty-one years. This probably represents a higher age than the average age of the college groups reported. Since in the population as a whole it is generally accepted that the incidence of tuberculous infection increases with age, this fact may explain the difference of incidence in the groups of students which have been compared.

The total incidence of tuberculous infection, as shown by positive tuberculin reactions, increased from 60 to 69.5 per cent for medical students, and from 54 to 58 per cent among nurses during their respective training periods. This increase was not as marked as that found by other observers.

The relatively small increase in the number of tuberculin reactors among students of medicine and nursing at Vanderbilt University may be explained by two factors. The first is that the number of tuberculous patients in the hospital is small as compared with the total number of patients treated. The other factor is that isolation technique in the care of tuberculous patients in the hospital is rigid. Further, the diagnosis of tuberculosis usually is established before the patient is admitted to the wards so that unrecognized cases rarely enter the hospital.

We were greatly impressed by the occurrence of negative tuberculin tests in some of the fourth-year medical students and student nurses who had shown positive tests in previous years. It has long been recognized that in the presence of advancing tuberculosis or acute intercurrent infection a positive tuberculin test may become negative. However, it has been quite generally accepted that in inactive tuberculous infection the tuberculin test usually remains positive. No mention of this reversal has been found in the literature dealing with tuberculin testing in college students. It is probable that the positive reactors were not retested.

Austrian (9) and Heimbeck (10) reported reversal of positive Pirquet

tests in children some years after the original test, though Herlitz (11) could not substantiate this. Geer (3) and Paretzky (12) have more recently published observations with respect to the reversal of positive Mantoux tests with the passage of time.

If a negative tuberculin reaction in an individual showing no clinical symptoms of tuberculosis is an indication of absence of tuberculous infection, then tuberculosis is not as often a permanent infection as has generally been supposed. If, on the other hand, the response to tuberculin of individuals with latent tuberculous infections varies between positive and negative from time to time, caution should be observed in interpreting negative reactions as evidence of the absence of tuberculous infection.

SUMMARY

1. The incidence of tuberculous infection in 555 medical students, of the School of Medicine of Vanderbilt University, as determined by positive tuberculin reactions to either 0.01, 0.1 or 1.0 mg. of Old Tuberculin, was found to be 60 per cent at the time of their admission to the medical school.

2. The incidence of positive tuberculin reactions in a group of 198 student nurses in the School of Nursing of Vanderbilt University, who were studied in a similar manner, was found to be 54 per cent.

3. Eighty per cent of the medical students and 90 per cent of the student nurses resided in the southern states prior to entering Vanderbilt University.

4. During the professional course, the total incidence of tuberculous infection increased from 60 to 69.5 per cent among medical students and from 54 to 58 per cent among the student nurses.

5. Twenty-one of the 102 medical students who gave positive tuberculin tests on admission to the medical school and who were subsequently retested became negative to 1.0 mg. of Old Tuberculin. Nine of the 37 student nurses who gave positive tuberculin tests on admission to the nursing school subsequently became negative to 1.0 mg. of Old Tuberculin.

REFERENCES

(1) Shepard, C. E.: Campaign against tuberculosis in college students, Am. J. Pub. Health, 1935, *25*, 1118.

(2) Heimbeck, J.: Tuberculous infection; attempts to prevent it by subcutaneous vaccination with BCG, Arch. Int. Med., 1931, *47*, 901.

(3) Geer, E. K.: Tuberculosis among nurses, Ibid., 1932, *49*, 77.

(4) HETHERINGTON, H. W., MCPHEDRAN, F. M., LANDIS, H. R. M., AND OPIE, E. L.: Tuberculosis in medical and college students, Ibid., 1931, *48*, 734.

(5) HETHERINGTON, H. W., MCPHEDRAN, F. M., LANDIS, H. R. M., AND OPIE, E. L.: Further study of tuberculosis among medical and other university students; occurrence and development of lesions during medical course, Ibid., 1935, *55*, 709.

(6) HERMAN, N. B., BAETJER, F. H., AND DOULL, J. A.: Tuberculous infection in medical students, Bull. Johns Hopkins Hosp., 1932, *51*, 41.

(7) LONG, E. R., AND SEIBERT, F. B.: The incidence of tuberculous infection in American college students; determination by standardized tuberculin (Purified Protein Derivative) on 18,744 college entrants in 1935–1936, J. A. M. A., 1937, *108*, 1761.

(8) LUMSDEN, L. L., AND DAUER, C. C.: Some features of tuberculosis mortality distribution in the United States, U. S. Treasury Dept., Public Health Bulletin No. 225, 1936.

(9) AUSTRIAN, C. R.: Evolution of tuberculous infection in childhood; observations on children admitted to dispensary over period of twelve years, Am. Rev. Tuberc., 1927, *16*, 501.

(10) HEIMBECK, J.: Immunity to tuberculosis, Arch. Int. Med., 1928, *41*, 336.

(11) HERLITZ, G.: Studien über die Prognose der okulten Kindertuberkulose. Eine Nachuntersuchung bei tuberkulinpositiven und tuberkulinnegativen Kindern, Acta paediat., Supplement II, 1937, *19*, 1.

(12) PARETZKY, M.: The disappearance of specific skin hypersensitiveness in tuberculosis; report based on 80 cases, Am. Rev. Tuberc., 1936, *33*, 370.

AN X-RAY STUDY OF THE ADULT RELIEF POPULATION OF A SMALL COMMUNITY[1]

D. O. N. LINDBERG[2]

Survey film studies of the chests of so-called healthy persons that include various racial and economic groups offer prospects for revealing roentgenographic changes in lesion characteristics, thus perhaps adding new factors to be considered in the problem of explaining the existing variation in mortality rates from pulmonary tuberculosis (1, 2, 3, 4). Such studies are, of course, dependent for their accuracy upon film quality and their proper interpretation (5, 6, 7).

As an example, in separate studies of 1,005 adult Negroes (8) and 705 white school teachers (9), only a slightly higher tuberculosis morbidity rate was recorded for the Negro although his mortality rate is actually 3.2 times greater than that for white persons (10). Outstanding were the observations of an unduly high incidence of clinically significant, nontuberculous disease of varying types, in the Negro, and a relatively low occurrence of inactive tuberculous lesions of the parenchyma among the teacher group. The Negro was thus found to harbor an untoward number of pulmonary tuberculous processes for potential reactivations, and especially so in the presence of coexisting chronic pulmonary affections which conceivably might precipitate focal reactions eventuating in the caseopneumonic lesions heretofore considered as characteristic of the response of nontuberculized races to tubercle bacilli.

The present X-ray study of the adult relief population of Macon County, Illinois, was suggested partly by the findings in these earlier special group examinations, and partly by recent statistical data, using Edwards's six major classifications of occupation, that pointed out a mortality rate for the unskilled worker three times that for clerks and two and one-half that of skilled workers (11).

The educational groundwork was laid by the local county tuberculosis

[1] Read before the joint session of the Mississippi Valley Sanatorium Association and the Mississippi Valley Conference, St. Louis, Missouri, September 22, 1938.

[2] Macon County Tuberculosis Sanatorium, Decatur, Illinois.

association over a period of approximately a year, and comprised a list of persons originally greater by 50 per cent than the number contemplated for actual examination. The film cost was met out of tax funds specially allotted for tuberculosis control purposes.

One thousand and fifty-four (1,054) adults between twenty and fifty years, on relief rolls for four years or longer, were filmed directly, that is, without any preliminary tuberculin testing, as was done in previous surveys involving relatively small adult groups.

Although females, ages twenty to forty, were included and no par-

TABLE 1

An X-ray study of the adult relief population, Macon County, Illinois—1937

AGES	NUMBER EXAMINED	SEX	MANIFEST TUBERCULOSIS					INFECTION			NONTUBERCULOUS FINDINGS (CLINICALLY SIGNIFICANT)	
			ACTIVE				INACTIVE					
			Minimal	Moderately advanced	Far advanced	All stages	Parenchymal fibrosis	Primary calcification*	Healed miliary	Total	Pulmonary	Cardiac
20–40	190	M	0	0	1	1	9	209	3	212	15	5
	231	F	3	1	0	4	10	232	3	235	11	22
Over 40	162	M	1	2	1	4	8	109	5	114	8	3
	202	F	1	0	0	1	3	55	2	57	7	4
All ages	524	M	1	2	2	5	17	318	8	326	23	8
	530	F	4	1	0	5	13	287	5	292	18	26
Total	1,054		5	3	2	10	30	605	13	618	41	34
Per cent			0.5	0.3	0.2	1.0	2.9	57.4	1.2	58.6	4.0	3.2

* As evidenced by healed Ghon foci (single or multiple) and calcified tracheobronchial lymph nodes.

ticular attention given to previous occupations, it was considered that the conditions of crowding, several families living as one, and with food limited to bare necessities, would make this group comparable, economically, to the low wage group of unskilled workers of more prosperous eras (12).

Of 1,054 persons examined, active parenchymal tuberculous lesions were found in 10, or 1.0 per cent, divided as follows: minimal, 0.5 per cent, moderately advanced, 0.3 per cent, and far advanced, 0.2 per cent. Definite parenchymal lesions of secondary, inactive types were observed in 30, or 2.9 per cent. The total disease incidence of parenchymal

TABLE 2

X-ray studies among special survey groups

	Number examined	Manifest tuberculosis					Nontuberculous findings* (clinically significant)	
		Active				Inactive		
		Minimal	Moderately advanced	Far advanced	All stages	Parenchymal fibrosis	Pulmonary	Cardiac
Adult relief group	1,054	5	3	2	10 (1.0%)	30 (2.9%)	41 (4.0%)	34 (3.2%)
Teachers	705	4	3	2	9 (1.3%)	17 (2.4%)	13 (1.8%)	49 (6.9%)
Adult Negroes	1,005	4	4	3	11 (1.1%)	43 (4.3%)	38 (3.8%)	154 (15.0%)
High school seniors	4,177	9	5	1	15 (0.4%)	10 (0.24%)	5 (1.2%)	34 (7.8%)
Total	6,941	22	15	8	45 (0.7%)	100 (1.4%)	97 (1.4%)	268 (3.8%)

* Data complete except for high school senior group which includes but 498 of those examined.

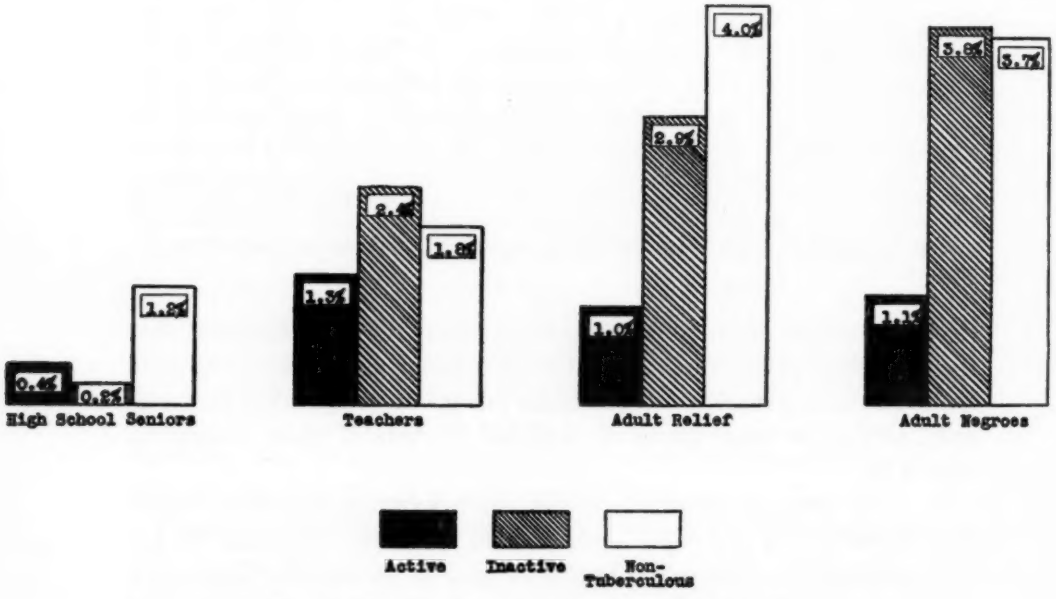

CHART 1. X-ray studies among special survey groups

tuberculosis, active and inactive, was, therefore, 3.9 per cent of those examined (table 1).

It should be noted that, just as in the case of the adult Negro survey, neither an untoward incidence of pulmonary tuberculosis nor a preponderance of exudative types of parenchymal shadows, extensive or otherwise, were encountered to explain the potentially high mortality for the lowest income groups. On the other hand, both Negroes and white groups on relief presented roentgenographic findings of an untoward incidence of inactive tuberculous lesions. That this incidence was relatively lower for the unskilled group might serve to explain their intermediary position between Negroes and the skilled white population in mortality curves.

Comparative data (table 2 and chart 1) seem to require explanation of the greater incidence of inactive, secondary tuberculous involvements of the lung parenchyma in the two groups with lowest living standards.

For the relief group, there is offered the theory that a relative rest regimen existed early in the period of economic chaos, which helped to fibrose many of the smaller active lesions. Then too, for the unemployed group there should be added the obvious reason that diagnoses are too often made, for the first time, when considerable disease extension has occurred, and because there is insufficient understanding of the necessity for early and uninterrupted treatment. As an example, of the group discovered with active tuberculosis, only 30 per cent realized the necessity for arresting their disease by the prompt acceptance of sanatorium supervision.

It becomes apparent from these findings that, while no more active tuberculosis was found to be present among the low wage classes in the era of economic depression than among other occupational groups, the problem of spread of infection over a longer ambulatory period, together with an inevitably increased mortality rate, commands our greatest efforts, largely educational, for the unskilled citizen.

CONCLUSIONS

1. In this study of 1,054 unemployed adults of both sexes between the ages of twenty and fifty, active tuberculous lesions were observed in roentgenograms, having reasonably good technical quality, in 1.0 per cent; inactive, 2.9 per cent, for a total morbidity incidence of approximately 4.0 per cent.

2. The incidence of active pulmonary tuberculosis among the relief population appeared the same as for the employed group.

3. Inactive lesions showed an increased incidence, somewhat paralleling those of other low living-standard groups as, for example, the employed Negro. It might be definitely expected that under unfavorable individual economic conditions reactivations would result in an increase of active lesions.

4. The higher mortality rate for the unskilled worker is accounted for, additionally, by the lack of education in the matter of accepting an adequate period of treatment, and at the same time suggests the need for earlier diagnosis.

REFERENCES

(1) Miller, J. A.: Some unsolved problems of tuberculosis, J. A. M. A., 1938, *111*, 111.
(2) McCain, P. P.: Tuberculosis among Negroes in the United States, Am. Rev. Tuberc., 1937, *35*, 25.
(3) Pinner, M.: Brief comment on race and tuberculosis, Ibid., 1937, *35*, 41.
(4) Lindberg, D. O. N.: A chest roentgen-ray study of the adult Negro population of an entire community, Ann. Int. Med., 1935, *8*, 1421.
(5) Brown, L.: A study of 503 cases of pulmonary tuberculosis with indefinite or no usual abnormal physical signs, Tr. Assn. Amer. Phys., 1931, *46*, 367.
(6) Lindberg, D. O. N.: Chest roentgenography—new standards and improved techniques, Illinois M. J., 1936, *70*, 415.
(7) McPhedran, F. M.: The roentgenogram in early tuberculosis in adults, U. S. Naval Med. Bull., 1932, *30*, 91.
(8) Lindberg, D. O. N.: A chest roentgen-ray study of the adult Negro population of an entire community, Ann. Int. Med., 1935, *8*, 1422.
(9) Lindberg, D. O. N.: The school teacher as a source of tuberculosis infection, Report of an X-ray study, Illinois M. J., 1935, *68*, 350.
(10) National Tuberculosis Association, Report of the Committee on Tuberculosis among Negroes: Tuberculosis mortality according to color, United States Registration Area, 1910–1934, 1937, p. 12.
(11) Whitney, Jessamine S.: Death rates by occupation, Natl. Tuberc. Assn., 1934, pp. 12, 17, 30.
(12) Statistical Bulletin, Metropolitan Life Insurance Company, No. 7, 1938, p. 4.

THE INCIDENCE OF TUBERCULOUS INFECTION IN STUDENT NURSES[1]

RUTH E. BOYNTON

This report presents the results of a study of the incidence of infection with tuberculosis as determined by a change from a negative to a positive tuberculin reaction in a group of students in the College of Education at the University of Minnesota, a group of student nurses on a general medical service at the University Hospital, and a group of student nurses on a special tuberculosis service in a tuberculosis sanatorium. All of the students in the three groups come from communities in and near Minnesota. While attending the University the nurses are all housed in modern dormitories where living conditions are of the best. Some of the students in the College of Education live in University dormitories, while others live in rooming houses, sorority houses or at home. The living conditions of the student nurses are better than for the students in the College of Education. Except for the difference in the type of education pursued at the University, the nursing group and the College of Education group are similar in all other respects.

Much has been written on the subject of tuberculosis among nurses, especially during the past ten years. The literature in this field has been summarized very thoroughly by Whitney (1). Although there are a few reports which seem to show that tuberculosis occurs no more frequently in nurses than in the general population, most of the evidence points to a much higher incidence of the disease in the nursing group. There still seems to be a difference of opinion, also, as to whether the incidence of tuberculosis is any greater among nurses employed in tuberculosis hospitals than in those working in general hospitals. This report makes no attempt to answer any of the above questions. No evidence is presented regarding the number of student nurses who develop clinical tuberculous disease, but rather data to show how many student nurses who were tuberculin-negative became infected, as shown by a change to a positive tuberculin reaction while working in a general

[1] From the Students' Health Service and Department of Preventive Medicine and Public Health, University of Minnesota, Minneapolis, Minnesota.

hospital and in a tuberculosis hospital, compared to a group of students on the same campus enrolled in the College of Education. Since infection with tubercle bacilli in most individuals produces a sensitization to tuberculoprotein, it can be determined fairly accurately by means of the intracutaneous tuberculin test whether an individual has become so sensitized as a result of tuberculous infection.

Students in the University of Minnesota School of Nursing are given tuberculin tests on admission to the School, and all negative reactors are retested annually thereafter. Students in the College of Education are given tuberculin tests on admission to the University, and the negative reactors are again tested in the last quarter of the senior year or approximately four years later. Beginning in April, 1933, in addition to the annual tuberculin test, those student nurses whose previous tests showed no reaction to tuberculin were given another tuberculin test within one week before going to the tuberculosis sanatorium for their special tuberculosis service. The length of the service in the sanatorium is six weeks. The students who were tuberculin-negative one week before going to the sanatorium were again retested one month after completing the tuberculosis service. Since it is generally assumed that sensitization to tuberculoprotein will occur within three or four weeks after infection, it was felt that the tuberculin test given one month after the completion of the tuberculosis service should pick up any students who had become tuberculin-positive as a result of infection incurred during the tuberculosis service.

For all groups tested the Mantoux intracutaneous technique was used, using Koch's Old Tuberculin. An initial dose of 0.01 mg. of OT was given. If there was no reaction to this a second test was done, using 1.0 mg. of OT.

Of 228 students who entered the College of Education in the years 1930 and 1931, 26.8 per cent had a positive tuberculin reaction. Of the 167 of this group who were tuberculin-negative in the freshman year, 149 were retested four years later in the senior year. Only one of the 149 had become tuberculin-positive during this four-year period, or 0.7 per cent.

In the group of student nurses entering the University School of Nursing during the years 1933 to 1937, 29.9 per cent showed a positive tuberculin reaction, approximately the same percentage as in the College of Education group. Of the 239 student nurses who were tuberculin-negative on admission, 41, or 17.9 per cent, became tuberculin-positive

when retested early in the second year of training. In the interval of time since admission these student nurses had spent three months on preliminary laboratory courses and the remainder of the time in the wards of the University Hospital or Minneapolis General Hospital caring for supposedly nontuberculous patients. Yet in a twelve months' period almost 18 per cent of the tuberculin-negative group had become infected with tubercle bacilli. Undoubtedly many patients with undiagnosed active tuberculosis are admitted to our general hospitals for surgery or emergency care and are a grave source of infection to the medical and nursing personnel who care for them. At the present time in both the University of Minnesota Hospital and the Minneapolis General Hospital all new admissions are given a tuberculin test and

TABLE 1

Incidence of tuberculous infection as shown by a change from a negative to a positive tuberculin reaction

	TOTAL NUMBER IN GROUP	PER CENT OF NEGATIVE REACTORS WHO BECAME TUBERCULIN-POSITIVE			
		Per cent	Time interval	All percentages based on a three-month interval	Ratio of infection rate
			months		
College of Education students.....	149	0.7	48	0.04	1.0
Student nurses—general medical service...	239	17.9	12	4.47	100.0
Student nurses—special tuberculosis service.	158	22.2	3	22.2	500.0

chest X-ray films are taken of those with positive tuberculin reactions. Such a plan should greatly reduce the tuberculosis infection rate of the personnel in these hospitals.

Tuberculin tests were given to student nurses one week before beginning a special tuberculosis service. Of 367 student nurses, 170, or 46.3 per cent, were tuberculin-negative within one week prior to beginning a six weeks' tuberculosis service. One month after completing this six weeks' service caring for tuberculous patients, 158 of the students who were negative to tuberculin at the time they started the service were retested. The time period between the two tuberculin tests was between eleven and twelve weeks. In this period, 35 of the 158, or 22.2 per cent, had become infected with tuberculosis as shown by a change from a negative to a positive tuberculin reaction.

A comparison of the incidence of tuberculous infection in these three groups of students is shown more clearly in table 1. Since the time interval between the first and second tuberculin tests was forty-eight months, twelve months and three months, respectively, in the three groups, in order to have a comparable time interval the percentages for each group were reduced to a three-month period. These figures are presented in column three of table 1. Arbitrarily taking the figure of 0.04 per cent for the College of Education as one and computing the ratio of infection rate for the two groups of student nurses, it is seen that the tuberculosis infection rate for student nurses on a general hospital service is 100 times as great, and for student nurses on a tuberculous service 500 times as great as for students in the College of Education.

SUMMARY

The incidence of tuberculous infection as evidenced by a change from a negative to a positive tuberculin reaction in students in the College of Education, student nurses on a general hospital service, and student nurses on a special tuberculosis service at the University of Minnesota is presented.

The tuberculosis infection rate is 100 times greater in the student nurses on a general hospital service than in students in the College of Education, and 500 times greater in student nurses on a special tuberculosis service than in College of Education students.

REFERENCE

(1) WHITNEY, JESSAMINE S.: Tuberculosis among nurses, A summary of the literature, Am. J. Nursing, 1935, *35*, 367.

SPONTANEOUSLY ACQUIRED TUBERCULOSIS IN RHESUS MONKEYS[1]

KENNETH C. SMITHBURN

In earlier publications we have reported our studies (1, 2) on the colonial morphology and virulence of tubercle bacilli isolated from various sources. Similar studies have been continued since these reports appeared, and among the many strains of tubercle bacilli isolated prior to January, 1938, 4 were from rhesus monkeys. The animals from which these 4 strains were isolated were in the colony of Dr. P. K. Olitsky to whom we are indebted for this and a part of the later material. Each of the four animals had acquired the disease spontaneously. When the pathogenic properties of these 4 strains were studied it was found that 3 of them were highly virulent for rabbits, as well as for guinea pigs. They were therefore of bovine type.

This high incidence of bovine type infection among the strains first isolated raised two questions: (*a*) whether this high incidence of bovine type infection is constant and, if so, how can it be explained when the incidence of bovine tuberculosis among cattle and among humans is so low in America; and (*b*) whether monkeys contract tuberculosis while under experimental observation, or prior to experimental use. Investigations were begun in January, 1938 to elucidate these two points and this report includes the observations made to date.[2]

MATERIALS AND METHODS

Whenever a monkey was discovered at necropsy to have had tuberculosis, a survey was made to ascertain, if possible, whether the primary lesion was situated in the respiratory or gastrointestinal system. Notes

[1] From the Laboratories of The Rockefeller Institute for Medical Research, New York City.

[2] We wish here to acknowledge and express gratitude for the generosity of Doctors P. K. Olitsky and A. B. Sabin of this Institute and of Doctors J. H. Bauer and L. T. Coggeshall of the International Health Division of the Rockefeller Foundation, who have made available to us the tissues of infected monkeys from their respective colonies, together with records of the infected animals.

were made on the distribution and extent of lesions, and blocks of infected viscera were saved for the preparation of histological sections. A portion of the most heavily infected viscus was reserved for animal inoculations and for making cultures.

Animal inoculations: A block of tissue, usually spleen or lung from the tuberculous monkey, was minced with sterile scissors, then ground in a mortar with sterile sand and sterile saline solution to make a heavy suspension, usually of about 20 per cent strength. Five cc. of this suspension were then centrifuged at very low speed for five minutes to throw down the largest particles, and the turbid supernatant was used for subcutaneous inoculation of guinea pigs. Each animal received about 2.0 cc. of the centrifuged suspension subcutaneously in the right groin. The suspensions were usually contaminated with other bacteria than tubercle bacilli, but none of the guinea pigs died from extraneous cause.

Cultures: To the remainder of the crude suspension of tissue from each diseased monkey was added an equal volume of 6 per cent (by weight) sulphuric acid and a few drops of bromthymol blue indicator. The flask containing this mixture was agitated and allowed to stand at room temperature. After thirty minutes or one hour the contents of the flask were brought to neutrality by adding 3 per cent sodium hydroxide. Several tubes of glycerolated egg-yolk medium (3) adjusted to pH 6.8 were seeded with about 0.25 cc. each of the neutral tissue suspension. The tubes were sealed with melted paraffin and incubated at 37°C.

In several instances some of the cultures so prepared were contamminated, either with postmortem invaders, or because necropsies were not done under aseptic conditions. For this reason each strain was also isolated after passage through a guinea pig. At a time after inoculation when one could be certain that the disease was established in the guinea pig (thirty to sixty days following inoculation) each was sacrificed and the spleen removed under aseptic conditions. About half the spleen was used to make cultures in the manner described above, except that the guinea pig tissues were exposed to sulphuric acid for only fifteen or twenty minutes.

When each strain had grown well, either in primary culture or after isolation from a guinea pig, it was transferred routinely on Corper's medium (3). Studies of the colony morphology were made on both the primary cultures and the stock cultures.

Typing of strains according to virulence: Four of the strains isolated in this study were typed by means of virulence tests. Two normal rabbits and two normal guinea pigs were each inoculated with 0.1 mg. of a stock culture of the strain to be tested. Rabbits were inoculated intravenously, guinea pigs subcutaneously. One rabbit and one guinea pig were sacrificed thirty days following inoculation, and all survivors at sixty days. Careful records were kept of the extent of lesions observed at autopsy, and microscopical surveys were also made to determine the extent of lesions. In this manner an approximation of the virulence of the organisms could be gained from the guinea pigs; and the progression or regression of lesions in rabbits indicated the type of the organisms (bovine if lesions progressed after thirty days, human type if regression occurred).

Typing of strains according to colonial morphology: We had observed previously (4) that the usual morphology of bovine tubercle bacilli grown on egg-yolk medium adjusted to pH 6.8 is smooth and glistening. When growth is massive the hemispherical contour is lost but the glistening, moist appearance remains and the margins of the growth are sharp and regular. Human type strains cultivated under identical conditions form colonies which are often quite round at the base, but dry and finely granular in consistency, and usually with elevated centres. Massive growths are also dry and finely granular, and from the edge of the growth a thin veil projects. Moreover, growth of human strains is, as a rule, more vigorous and profuse.

Using the criteria described above, we examined as unknowns a large number of subcultures of strains of known type and found that the type of organisms could be ascertained with a very considerable degree of certainty. Accordingly the primary cultures isolated in this study, either directly from monkeys or after passage through a guinea pig, together with the stock subcultures of each strain, were examined with a magnifying glass and type determinations were made. In each instance the type determination on the primary cultures agreed with similar determinations on the stock cultures. Such studies were made after three or four weeks' incubation as it was previously found (4) that studies made later were subject to changes and were less reliable.

VIRULENCE OF THE STRAINS ISOLATED FROM MONKEYS

The virulence of three strains has not been determined except as they induced progressive disease in monkeys. Each of the 4 strains which

were inoculated into rabbits and guinea pigs were fully virulent for guinea pigs, and 3 of them were fully virulent for rabbits also. Eleven additional strains were each inoculated into two guinea pigs. One strain (6262, table 1) proved to be of substandard virulence, while the remaining 10 strains were fully pathogenic for cavies. The approximate virulence of the 15 strains so studied is shown in table 1.

In the case of strain 6127 the tissues of the monkey from which the strain was isolated were heavily laden with acid-fast bacteria. The organisms were present in such numbers that they could be seen in sections with the low power lens (× 150). The lesions in this monkey were massively caseous. One of the two guinea pigs inoculated with the suspension of spleen from this monkey was sacrificed after thirty days and exhibited rather extensive pulmonary, hepatic and splenic lesions

TABLE 1

Relative virulence of 15 strains of tubercle bacilli isolated from monkeys

	STRAIN NUMBER														
	3103	4540	4861	4892	6127	6187	6240	6241	6242	6258	6259	6262	6263	6293	6373
Virulence in guinea pigs	4+	4+	4+	4+	4+*	4+	4+	4+	4+	4+	4+	2+	4+	4+	4+
Virulence in rabbits	±	4+	4+	4+	†	†	†	†	†	†	†	†	†	†	†

4+ indicates highly pathogenic, 2+ indicates moderately pathogenic, ± indicates very slightly pathogenic (no progressive disease).

* See remarks in text regarding pathogenic properties of this strain.

† Indicates test not done.

with extensive caseation and numerous acid-fast bacilli in the lesions. The second guinea pig succumbed on the fifty-fourth day following inoculation and exhibited extensive lesions in spleen, lungs, liver and lymph nodes. The lesions seen microscopically were not epithelioid cell tubercles but were small aggregations of free and phagocytosed neutrophils and phagocytic mononuclears, each bearing many acid-fast bacilli. In the lungs these collections of cells were intraälveolar, and the bordering alveolar septa showed no change other than slight vascular dilatation. But the cells within the alveoli showed marked degenerative change, and, as in the monkey from which the strain originated, the acid-fast organisms were so numerous they could be seen at low magnification. These findings are detailed because of the extraordinary pathological picture induced by strain 6127.

TYPES OF MYCOBACTERIA RECOVERED FROM MONKEYS

The type of 4 strains was determined by inoculation of rabbits and guinea pigs. Fourteen additional strains were isolated from as many monkeys and were typed according to their colonial morphology. Regarding the 4 strains typed by virulence, the result is quite certain. In the case of the strains typed by colonial morphology, the result is presumably, though not certainly, correct in every instance. Table 2

TABLE 2

Cultural characteristics and type of each of 18 strains of tubercle bacilli isolated from 18 rhesus monkeys

STRAIN FROM RHESUS NUMBER	VIGOR OF GROWTH	PREDOMINANT COLONY FORM	MANNER OF TYPING	TYPE OF STRAIN
3103*	Excellent	FS†	Virulence	Human
4540	Fair	S	Virulence	Bovine
4861	Fair	S	Virulence	Bovine
4892	Fair	S	Virulence	Bovine
6127	Poor	S	Cultural characteristics	Bovine
6187	Excellent	FS	Cultural characteristics	Human
6240	Fair	FS	Cultural characteristics	Human
6241	Fair	FS	Cultural characteristics	Human
6242	Fair	S	Cultural characteristics	Bovine
6258	Poor	S	Cultural characteristics	Bovine
6259	Good	FS	Cultural characteristics	Human
6262	Good	FS + R	Cultural characteristics	Human
6263	Good	FS	Cultural characteristics	Human
6293	Poor	S	Cultural characteristics	Bovine
6373	Poor	S	Cultural characteristics	Bovine
6422	Excellent	FS + R	Cultural characteristics	Human
6423	Good	FS + R	Cultural characteristics	Human
6424	Good	S	Cultural characteristics	Bovine

* These are serial numbers used over a period of many years.

† FS indicates flat spreading granular colonies, S indicates smooth, and R indicates coarsely granular rough colonies.

shows the type of the 18 strains, together with their cultural characteristics. The first 4 strains included in table 2 were those typed by virulence tests.

Table 2 shows that between the bovine and human type strains there were differences in both colony form and growth energy.

This result shows that the incidence of bovine type infection among the 18 rhesus monkeys was 50 per cent. While this figure cannot be re-

garded as rigidly accurate since the type of each strain was not determined by inoculation of animals, the incidence is certainly much higher than the incidence of bovine type infections among human beings in America. Moreover, the high incidence of bovine infection could not be accounted for on the basis of the diet supplied to the animals after arrival in the United States, since herd-testing and pasteurization of the milk supply is practiced. The obvious assumption was, therefore, that at least a part of the monkeys contracted tuberculosis before arrival in this country. Subsequent evidence will be offered to substantiate this assumption.

TIME WHEN DISEASE WAS ACQUIRED BY MONKEYS

Obviously it was not possible to ascertain in every instance whether monkeys contracted tuberculosis in the laboratories or elsewhere. But in four animals from which tubercle bacilli were isolated we had available the complete histories from the date of their arrival by steamship. These animals, 6242, 6258, 6262 and 6263 (table 2), arrived by boat at New York on December 28, 1937. They were received by the dealer, transported by him to this Institute on January 4, 1938, and were included in a group of forty-five monkeys received by Dr. P. K. Olitsky and Dr. A. B. Sabin. The discovery of tuberculosis in three of them (6258, 6262 and 6263) was incidental to the necropsy following other experimental procedures, that is, the animals did not die as a result of tuberculosis. In rhesus 6258 the pulmonary lesions had already advanced to cavitation, and in 6263 there was a large, firm but fluctuant tuberculous abscess at the ileocaecal junction. These lesions were certainly not fresh ones, yet rhesus 6258 and 6263 had arrived at New York only thirty-four and thirty-seven days prior to the time the lesions were found. Rhesus 6262, sacrificed thirty-six days after arrival, exhibited lesions in the gut, mesentery, omentum, spleen, liver and lungs. The oldest lesions were in the liver and lungs. More convincing still is the record of rhesus 6242. This animal was kept on a normal diet and subjected to no experimental procedure, yet died on January 25, 1938, just twenty-eight days after arrival in the United States. Emaciation was marked. At autopsy two chronic tuberculous lesions were found in the lung. Opposite one of these there was a dense fibrous adhesion to the parietal pleura. One lesion was caseous; the other had advanced to the fluid state. Tubercle bacilli were numerous in the lesions.

As further evidence that at least some of the animals were infected with tuberculosis prior to entry to America is the fact that in six of twelve instances, in which the primary lesions could be ascertained,[3] this was in the gastrointestinal tract. This would seem to point to a contaminated food supply. Monkeys in this Institute are given a diet consisting of pasteurized milk, bread, bananas, oranges, peanuts and carrots. Moreover, the handlers are healthy and apparently free of tuberculosis, so that it would seem probable that the infections were acquired elsewhere.

These results make it seem highly probable that a certain percentage of laboratory monkeys which have tuberculosis acquire the disease before arrival in America. In transit or in the animal quarters of the laboratories they may infect other animals by coughing or otherwise; but in a small survey it appears that about 9 per cent of animals of a given lot (4 of 45) were tuberculous on arrival.

DISCUSSION

One of the primary requisites for experimental investigations is dependable animal stock. The existence of tuberculosis may significantly influence the course of events in animals being used for dietary studies, or investigations of other diseases, or even in physiological experimentation. The rhesus monkey is essential for investigation in certain fields. This animal has been known to be highly susceptible to tuberculosis, yet is said to be rarely if ever infected with tuberculosis when in the wild state. The results we have obtained indicate, however, that a considerable number of monkeys may become infected with tuberculosis before they reach America. Obviously a useful purpose would be served if tuberculosis-free stock were available for experimental use.

However important a tuberculosis-free supply of monkeys would be to medical research, it would seem even more important that the potential public health hazard of the tuberculous monkey be studied. Our observations indicate that pulmonary lesions in monkeys frequently cavitate; they must expel many bacteria with their coughing. It is reasonable to assume that if monkeys imported for research purposes

[3] In all of the monkeys of this series lesions were present in lungs as well as in abdominal viscera. It was not possible in all cases to discover the primary lesion. But when there was a large, old lesion in the gastrointestinal system and only miliary lesions in the lung, the lesion was considered to have originated in the former.

are tuberculous, so also are monkeys imported for exhibition in our large public zoological gardens. Then, unless adequate precautions are taken, tuberculous monkeys are placed on exhibition in overcrowded cities and visited by throngs which include many undernourished children—fertile soil for continued proliferation of mycobacteria. Indeed it may well be that the rhesus monkey is the source of the small residuum of bovine tuberculosis in our cities, and of a certain additional percentage of human type infections. Of these facts some pathologists in our zoos are well aware. Fox (5) discusses at length the existence of tuberculosis in monkeys, and describes methods for its control which have been successful in the Philadelphia Zoo. Schroeder (6) has recently written on the subject. He pointed to the fact that primates in the wild are free of tuberculosis, that heavy exposure, beginning immediately with capture, continues during transit and while animals are retained by dealers. He emphasized the hazard to the monkey of uncontrolled exhibition in public places but failed to point out the hazard of the monkey to man, although he stated that in primates in captivity the mortality rate from tuberculosis is two hundred times that in man. Therefore it would seem that rigorous steps are justified in order to prevent the importation of tuberculous monkeys. Health measures instituted at the source of origin and regulations governing the shipment and handling of monkeys by dealers might accomplish the desired effect.

SUMMARY

Eighteen strains of tubercle bacilli were isolated from as many cases of spontaneously acquired tuberculosis in rhesus monkeys. In about half the monkeys the primary lesion was apparently in the gastrointestinal tract. Fifty per cent of the strains were of bovine type. Evidence was gathered which indicates that a portion, at least, of the animals were tuberculous when imported.

The importation of tuberculous monkeys for zoological exhibition may constitute a public health hazard.

REFERENCES

(1) SMITHBURN, K. C.: J. Exper. Med., 1935, *61*, 395.
(2) SMITHBURN, K. C.: Ibid., 1935, *62*, 645.
(3) CORPER, H. J., AND COHN, M. L.: Am. J. Hyg., 1933, *18*, 1.
(4) SMITHBURN, K. C.: J. Exper. Med., 1936, *63*, 95.
(5) FOX, H.: Diseases in captive wild animals and birds, Philadelphia, J. B. Lippincott, 1923.
(6) SCHROEDER, C. R.: Am. J. Pub. Health, 1938, *28*, 469.

PULMONARY TUBERCULOSIS IN THE SECOND DECADE OF LIFE[1]

I. Its Development and Fatality

DAVID ZACKS

A certain proportion[2] of children who survive an initial tuberculous infection in their first decade of life begin to develop subsequent disseminations or reinfections during their second decade of life. These disseminations or reinfections usually begin as minimal lesions and are encountered clinically in two phases, the symptomatic and the asymptomatic. If we wait for the patient to come to the office the great majority will present symptoms. In case-finding surveys, with routine X-ray films of tuberculin-positive children, we found that in the first stages of development pulmonary tuberculosis rarely has an acute onset. The disease in its chronic form always has an insidious, symptomless beginning, the only objective evidence being a chance X-ray finding which may, however, reveal fairly extensive lesions. In the great majority of instances the lesions are apical and vary in extent in their relation to the anterior or posterior ribs. In its acute form, pneumonic phthisis which occurred in 2 of 536 cases, the diagnosis at first was nonspecific pneumonia. Those who have had an opportunity to observe these asymptomatic lesions by serial X-ray films have been indelibly impressed by their tendency to spread without symptoms, without signs, until sooner or later a considerable lung area is involved.

During the course of development and spread, no gross retardation in growth occurs in growing children. In only 4 per cent of the instances was the weight observed to become stationary with the appearance of the lesion. A cavity may develop without any objective or subjective symptoms. If a child is in a sanatorium where the temperature is observed periodically, cavity formation may be found to be accompanied by slight or moderate fever. If put to bed the patient will gain weight rapidly, the pseudo-recovery of Laennec, while the X-ray shows persistent exten-

[1] From the Massachusetts Department of Public Health, Boston, Massachusetts.

[2] The exact proportion is being determined for a large group of children and will be reported later.

sion of the lesion in the majority of cases. An extensive haematogenous spread may occur without any symptoms. A bronchogenic spread, the result of a spill from a cavity, is usually accompanied by fever, symptoms and signs. A haemorrhagic spread will give signs, symptoms and toxaemia. There comes a time, however, when symptoms make their appearance in the slowly spreading lesions. The average interval of time for this to happen is three years, the younger the age at diagnosis the slower the spread and the longer the period of time. Toxic symptoms may not appear until shortly before death.

This clinical study is based on 536 white children who were observed carefully for a period of 2,144 person years[3] or an average of four person years. The longest period of observation was twelve years, the shortest period was one year.

The material came from two sources. The larger group, 443 children (137 boys and 306 girls) were discovered in the public schools. Of these, 297 were found in the schools as a result of the routine X-raying of Pirquet positive children, and 146 developed pulmonary tuberculosis during the course of observation of a large group of school children who were followed annually with check-up X-ray examinations. A smaller group consisting of 93 patients were originally tested at the school clinics but were not followed routinely. These, however, were subsequently reported as pulmonary tuberculosis, either by county clinics or private physicians, and were included in this study after the diagnosis was confirmed.

DESCRIPTION OF THE GROUP AT THE BEGINNING OF THE STUDY

In the 536 children were 367 girls and 169 boys, approximately two girls to each boy; 63.6 per cent had familial contact. The cumulative tuberculosis mortality in these contact families was 38.8 per cent, the case fatality 44.3 per cent (41 per cent males and 45.5 per cent females). Nineteen were in the age group five to nine years, 208 in the age group ten to fourteen years, 285 in the age group fifteen to nineteen years, and 24 in the age group twenty years and over. It is noteworthy that of the 93 reported cases 83.9 per cent were in the older age group fifteen years or more, whereas, in the school group, 52.1 per cent were in this age group; 35.5 per cent of the entire group had symptoms and/or signs referable to the chest and 12.9 per cent had positive sputum

[3] A person year represents the experience of one person or patient who was observed for one year.

(boys 10.7 per cent and girls 13.9 per cent); 13.9 per cent of the entire group had cavities (boys 1.2 per cent and girls 14.8 per cent).

The school clinic group, 443 children, were all in school and presumably well. In this group the diagnosis was made exclusively on X-ray evidence in 72.5 per cent, and in only 27.5 per cent was the X-ray diagnosis supported by symptoms and/or signs referable to the chest at the time of the examination and could properly be classified as so-called "manifest disease." In the school group, sputum was positive in 6.8 per cent (3.6 per cent boys and 8.3 per cent girls).

In the reported group of 93 children, 73.1 per cent already had symptoms and/or signs referable to the chest at the time of diagnosis, as well as more extensive lesions on X-ray. In this group positive sputum was found in 41.9 per cent (40.6 per cent boys and 42.6 per cent girls).

The X-ray classification of the whole group by topography of lesions is given in table 1. The classification is based on 531 children, as the location and extent of the original lesion was unknown in 5 children.

As the shadow cast on the roentgenogram is the main reliance in diagnosis for tuberculin-positive but otherwise presumably healthy school children, the classification of these shadows according to their extent and location was found to be extremely helpful and practical. A qualitative description of these lesions, such as exudative, productive, caseous-pneumonic, is not possible with any degree of accuracy from the first film alone. The terms "progressive" and "retrogressive" are more significant in describing the course of these lesions.

Apical lesions, soft in appearance, are either homogeneous or mottled, with a fine or coarse stippling; or hard, strand-like or stringy, and may or may not be accompanied (or preceded) by calcified nodes in the parenchyma or tracheobronchial region. Such apical lesions are almost always aetiologically tuberculous. The differential diagnosis is an occasional upper lobe atelectasis, bronchiectasis or lung abscess; very rarely, congenital cystic disease, if this is confined to one or both upper lobes.

Sub- or infraclavicular shadows must be distinguished from an acute or subacute nonspecific pneumonia, which is not infrequently found in children who are able to attend school. In appearance, the transient shadow is not dissimilar to its chronic counterpart. There is almost always, however, a history of an acute "cold" or "grippe," not severe enough to confine the patient to bed. A second film which should always be made within ten days or two weeks will show either a complete

TABLE 1

Topography of original X-ray lesions of 167 boys and 364 girls by age groups

Age Group	6 to 9 years				10 to 14 years				15 + years				6 to 15 years				Total lesions	
Sex	M	Per cent	F	Per cent	M	Per cent	F	Per cent	M	Per cent	F	Per cent	M	Per cent	F	Per cent	Number	Per cent
Subclavicular	0	0	1	9	5	8	21	15	11	12	30	14	16	10	52	14	68	13
Unilateral:																		
Apex above clavicle	3	38	5	46	16	25	36	25	21	22	43	21	40	24	84	23	124	23
To second anterior rib	1	12	2	18	13	20	25	17	15	16	33	16	29	17	60	17	89	17
Beyond second anterior rib	1	13	1	9	8	13	16	11	5	5	17	8	14	9	34	9	48	9
Unilateral with cavity	0	0	0	0	2	3	4	3	5	5	18	8	7	4	22	6	29	5
Total	5	63	8	73	39	61	81	56	46	48	111	53	90	54	200	55	290	54
Bilateral:																		
Apices above clavicles	3	37	2	18	10	16	15	10	16	17	18	9	29	17	35	10	64	12
To second anterior ribs	0	0	0	0	8	12	12	8	4	4	10	5	12	7	22	6	34	6
Beyond second anterior ribs	0	0	0	0	1	1	10	7	6	6	13	6	7	4	23	6	30	6
Bilateral with cavity	0	0	0	0	1	2	5	4	12	13	27	13	13	8	32	9	45	9
Total	3	37	2	18	20	31	42	29	38	40	68	33	61	36	112	31	173	33
All lesions	8	100	11	100	64	100	144	100	95	100	209	100	167*	100	364*	100	531*	100

* Five children, 2 boys and 3 girls, not included because location and extent of original lesion unknown.

disappearance of the "fleeting shadows" or considerable clearing. The specific chronic shadow will persist. These lesions must also be differentiated from interlobar pleural effusion which upon clearing leaves a thickened interlobar fissure. Atelectasis, due to bronchial obstruction by foreign body, or large tracheobronchial node and pulmonary abscess must also be kept in mind.

Unilateral basal shadows are usually, and bilateral shadows almost always nontuberculous. The diagnosis in the great majority of instances is bronchiectasis or atelectasis, or a combination of both. There is usually a story of long standing cough with loose expectoration which is persistently negative for tubercle bacilli. Râles are easily elicited in either one or both bases. Basal bronchiectasis is not infrequently found in school children. Basal tuberculosis is rare.

Table 1 shows that 12.8 per cent of all the lesions were sub- or infraclavicular, either uni- or bilateral, and 87.2 per cent were apical; 54.6 per cent of the apical lesions were unilateral, 5.5 per cent with cavities. The majority of the unilateral apical lesions were of minimal extent, that is, either above the clavicle within the first anterior rib, or from the apex down to the second anterior rib. Bilateral apical lesions were present in 32.6 per cent of the cases, 8.5 per cent with cavities. It should be noted that the older the age group the more advanced were the lesions on the original diagnosis, particularly in the bilateral lesions. For instance, bilateral lesions extending below the second anterior ribs and lesions with cavities occurred in 10 per cent (2 of 20) of the boys in the age group ten to fourteen years, against 47.4 per cent (18 of 38) in the age group fifteen or more years. For girls in the age group ten to fourteen years, the incidence of advanced lesions was 47.4 per cent (15 of 42) contrasted with 58.8 per cent (40 of 68) in the age group fifteen or more years (see table 1).

COURSE OF PULMONARY LESIONS

As these soft lesions were observed with serial films over a period of time, the majority showed progression, some definitely retrogressed, and some remained stationary. If such a lesion is observed early in the development (case 10, plate 4) it may be seen to spread at first and involve a certain area, then it may show retrogressive changes. On the other hand, a shadow which is definitely retrogressive at first, even to the point of partial calcification, may reactivate and progress to a fatal termination (case 11, plate 4). Stationary shadows, homogeneous or

mottled in character, may remain stationary for a longer or shorter time, then begin to spread or retrogress. Soft stationary shadows are always uncertain as to outcome until definite changes occur which will indicate their behavior. Strand-like or stringy shadows, either apical or subclavicular, tend to remain stationary for a long time with rare exceptions and, after puberty has passed, may remain stable.

Lesions of minimal extent that progress do so on the whole rather slowly and silently. If apical, the spread is downward as if by contiguity, first on the affected side, then on the contralateral side if this is not already involved. If bilateral, both sides may spread simultaneously. When a cavity spills over, the consequent bronchogenic dissemination may be rapid indeed. Occasionally, a small lesion either apical or subclavicular has a sudden rapid spread to both lung fields which can be explained only by haematogenous or lymphatic dissemination. When this appears, both lung fields are spotted with innumerable shadows of fine or coarse stippling. Subclavicular lesions on the whole tend to spread more rapidly and develop cavities more often and more quickly than apical lesions of similar minimal extent. The spread in subclavicular lesions is usually downward, but it may go in either direction.

The proportion of X-ray spread of apical lesions by age groups is not significantly different, but the period of observation is longer for the younger age groups because the younger the child at diagnosis, the slower the rate of spread. The average years of observation for the age group five to nine years was seven years; for the age group ten to fourteen years, five years; and for the age group fifteen or more years, three years.

The first thing to note in table 2 is the direct relationship of the extent of the apical lesions to mortality; the more advanced lesions give the greatest mortality during a shorter period of observation. After an average of four years, all X-ray lesions showed a spread in 63.1 per cent; 24.3 per cent retrogressed, and 7 per cent remained stationary; 5 per cent of the lesions that spread according to X-ray observation first showed a tendency to retrogress, but finally spread (case 11, plate 4). Nine per cent of the lesions that eventually retrogressed were also observed during their initial spreading phase (case 10, plate 4).

Of the children showing progressive lesions by serial X-ray films, 35.2 per cent have died within the period of observation (23.8 per cent of the boys and 40.7 per cent of the girls). The excess mortality for the

TABLE 2

Progress of tuberculosis lesions by topography of lesions at diagnosis

LOCATION AND EXTENT OF LESIONS BY X-RAY AT DIAGNOSIS	NUMBER		MEAN YEARS OF OBSERVATION		PER CENT DEAD OF TOTAL		RESULT ON X-RAY AT THE END OF FOLLOW-UP PERIOD									
							Per cent progressive		Per cent dead of progressive		Per cent retrogressive		Per cent stationary		Per cent unknown	
	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F
Subclavicular lesions	16	52	3.4	3.8	6.3	17.3	87.5	63.4	7.1	27.2	6.2	30.8	6.2	1.9	0	3.8
Unilateral:																
Apex above clavicle	40	84	4.5	4.1	5.0	10.7	50.0	50.0	10.0	21.4	30.0	29.7	12.5	13.1	7.5	7.1
Apex to second anterior rib	29	60	4.6	4.8	13.8	16.7	58.6	45.0	23.5	37.0	34.5	46.6	3.4	5.0	3.4	3.3
Apex beyond second anterior rib	14	34	3.9	4.5	14.3	38.2	92.8	73.5	15.3	52.0	7.1	23.5	0	0	0	2.9
Unilateral with cavity	7	22	3.8	2.8	28.6	22.7	85.7	77.2	33.3	29.4	14.2	9.1	0	13.6	0	0
Bilateral:																
Apices above clavicles	29	35	4.4	4.6	6.9	11.4	44.8	48.5	15.3	23.5	27.6	22.8	10.3	14.3	17.2	14.3
Apices to second anterior ribs	12	22	4.8	4.5	33.3	31.8	66.7	68.1	50.0	46.6	16.6	13.6	0	18.2	16.6	0
Apices to beyond second anterior ribs	7	23	2.9	3.3	57.1	69.6	100.0	86.9	57.1	80.0	0	8.7	0	0	0	4.3
Bilateral with cavity	13	32	1.7	2.5	38.5	59.4	84.6	93.7	45.5	63.3	7.7	3.1	0	0	7.7	3.1
All lesions	167	364	4.0	4.0	15.6	25.3	65.2	62.0	23.8	40.7	21.6	25.6	6.0	7.4	7.2	4.9
All lesions combined	531*		4.0		22.2		63.1		35.2		24.3		7.0		5.6	

* Five (5) children, 2 boys and 3 girls, not included because original lesion unknown.

girls is due partly to the fact that they had more extensive lesions at the time of the original diagnosis (table 1), had a greater proportion of cavities and developed cavities and postitive sputum more frequently. The girls developed cavities at a rate of 4.9 per cent a year; the boys, 3.7 per cent a year. The rate of the development of cavities by the topography of the lesions was as follows:

Subclavicular: boys, 7.4 per cent a year; girls 6 per cent a year
One apex above clavicle: boys, 1.1 per cent a year; girls 4.0 per cent a year
Both apices above clavicle: boys, 2.4 per cent a year; girls 4.3 per cent a year
One apex to second anterior rib: boys, 3.0 per cent a year; girls 2.1 per cent a year
Both apices to second anterior ribs: boys, 6.9 per cent a year; girls 5.0 per cent a year
One apex to beyond second anterior rib: boys, 9.3 per cent a year; girls, 7.2 per cent a year
Both apices to beyond second anterior ribs: boys, 4.9 per cent a year; girls 13.2 per cent a year

PROGRESSIVE VERSUS RETROGRESSIVE LESIONS

Is it possible to foretell, once a lesion has been determined to be tuberculous, whether it will progress, retrogress or remain stationary? This is an important question in prognosis and when an attack upon an early lesion by collapse therapy is being considered. Lesions that tend to retrogress on the whole do well. Lesions that show steady progression, no matter how slowly, ultimately do poorly. This brings us face to face with the enigma of the shadow due to the primary infiltrate, which, on the whole, retrogresses; and the shadows due to secondary disseminations or reinfections which we have seen to progress in 2 out of every 3 cases. Unfortunately, from the X-ray appearance of the shadow itself, when not accompanied by definitely visible calcified tracheobronchial nodes, it cannot be ascertained in the first film whether the lesion is a primary infiltrate or a shadow due to a secondary dissemination or reinfection. When calcified tracheobronchial nodes either accompany or precede the soft shadow, it is usually certain at least that we are dealing with secondary dissemination or reinfection tuberculosis, but the behavior of the individual lesion can be determined only by serial films. In answering this question, then, there must be considered in addition to the character of the shadow certain other factors, namely,

the age of the patient, accompanying or preceding calcified tracheobronchial nodes and the tuberculin test.

A: Given a positive tuberculin test simultaneous with the discovery of the lesion:

1. In the age group five to nine years, a soft sub- or infraclavicular shadow will as a rule behave like a primary infiltrate, will subside sooner or later, with or without treatment, and will usually leave in its place residual calcified nodes or strand-like shadows or both. No lesions of this character in boys were included in this study. The one lesion included was a girl, seven years of age, whose lesion, however, showed retrogressive changes at first, then began to progress and behave like an "adult-type" lesion. Apical lesions in the first decade of life, homogeneous in character and unaccompanied by calcified nodes, also tend to resolve (case 7, figures G and G_1, plate 3). Apical lesions in this age group, soft in appearance and accompanied by calcified nodes, tend to spread and disseminate (case 3, figures C and C_1, plate 1). Eight boys of this age group with apical lesions were included in this study. Of these, 5 had progressed with two deaths and 3 had retrogressed at the end of 6.5 mean years of observation. Of the 10 girls in the first decade of life with apical lesions, 5 had progressed with one death, 3 had retrogressed, and 2 remained stationary at the end of 6.7 mean years of observation. The rate of progression is extremely slow for the children in this age group.

2. In the second decade of life, soft lesions, subclavicular or apical, homogeneous or mottled, accompanied by calcified tracheobronchial nodes or not, will, in the majority of instances, progress; that is to say, two out of every three will progress (see plates 1, 2 and 3). The only way to determine their behavior is by serial X-ray films. A soft lesion may remain stationary for a time but this fact should not deceive us. These lesions should never be dismissed as clinically unimportant even in the absence of symptoms or signs.

B: If the tuberculin test is known to be definitely negative immediately before the specific process in the lungs develops and becomes positive at the time of the discovery of the lesion, the shadow is due to the primary infiltrate in any age.

C: A hard, strand-like or stringy shadow in any location will, with rare exceptions, remain stationary during puberty and may be dismissed as unimportant after puberty has passed.

CHANGES WHICH OCCURRED IN THE GROUP AT THE END OF FOUR MEAN YEARS OF OBSERVATION

1. Two-thirds of the cases have progressed according to X-ray observation.

2. Of the patients with asymptomatic lesions 44.5 per cent have developed symptoms and/or signs. The average interval between the first X-ray film and appearance of clinical symptoms was three years. The rate of development was 10 per cent a year.

PLATE 1

FIGS. A & A_1. Progressive lesion. Case 1. R. J. M. Boy, thirteen years and four months old, weight 90 pounds, height 60 inches. Average weight. Asymptomatic. Initial film A: May, 1934. Calcified node right apex. Left apex, calcified node and homogeneous shadow occupying less than one-half the apex above the first anterior rib. By March, 1935, slow spread to third left anterior rib with small cavity in apex. Serial film A_1: February, 1936. Mottled shadow has extended through left lung field. Right top, calcified nodes as in 1934, but in addition a hazy shadow in extreme apex. Weight 120 pounds, height 66 inches. Became symptomatic in January, 1936, and sputum-positive in March, 1936. From May to December, 1936 in sanatorium under collapse therapy.

FIGS. B & B_1. Progressive lesion. Case 2. F. I. Girl, eleven years and nine months old, weight 72 pounds, height 57 inches. Ten per cent underweight. Initial film B: February, 1929. Homogeneous shadow occupying less than one-half of right apex above clavicle, mesially, and along upper mediastinum to right of hilum; calcified nodes in right hilum. Left: perihilar shadow with calcified and small calcified node in first left anterior interspace. By 1931 spread to second right anterior rib. Now râles and symptoms but consultant does not agree with sanatorium recommendation. From 1932 to 1934 slowly progressive lesion in right with cavity. In 1932 contralateral spread left top and left midlung. Weight 100 pounds in 1932, 109 pounds in 1934, then stationary. Serial film B_1: March, 1935. Bilateral disseminated coarse mottled shadows occupying more than two-thirds of both upper lung fields. From April to September, 1936 in sanatorium under bilateral collapse. Denies symptoms and no sputum available for examination.

FIGS. C & C_1. Progressive lesion. Case 3. T. R. Boy, nine years and one month old, weight 55 pounds, height 49.6 inches. Average weight. Initial film C: 1925. Homogeneous shadow both apices above first anterior ribs. Calcified node in right apex and two or three calcified nodes in right base. Left hilum moderately dense without definite calcification. Questionable calcified node in first left anterior interspace. From 1926 to 1928 refused examination because consultant gave an opinion that there was nothing clinically wrong with the boy at this time; the lesion at top of right lung being old and causing no symptoms, it is entirely inactive, no fever, no moisture. From 1929 to 1930 bilateral X-ray spread to second anterior ribs with small cavity in right apex and questionable cavity in first left anterior interspace. Serial film C_1: November, 1931. Coarse and fine mottled shadows in both lung fields to third anterior ribs, more marked on right. Cavity in first right anterior interspace. Question of cavity in first left anterior space. Weight 116 pounds, height 66.5 inches; seven per cent below average. Symptomatic with slight fever, 99.6° to 100.2° F.; then rapid decline to October, 1932, when he died. Duration of life, seven years and four months.

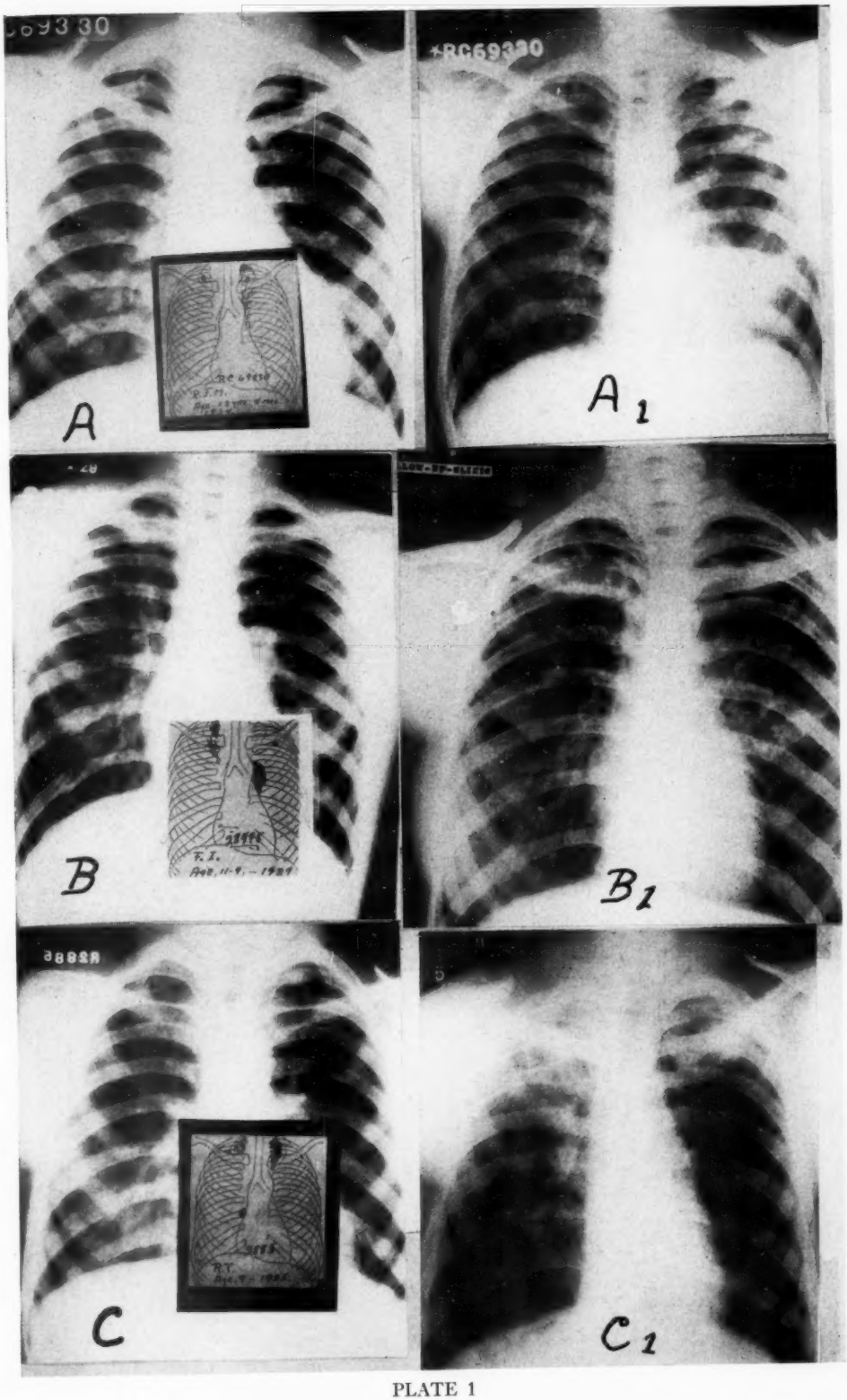

PLATE 1

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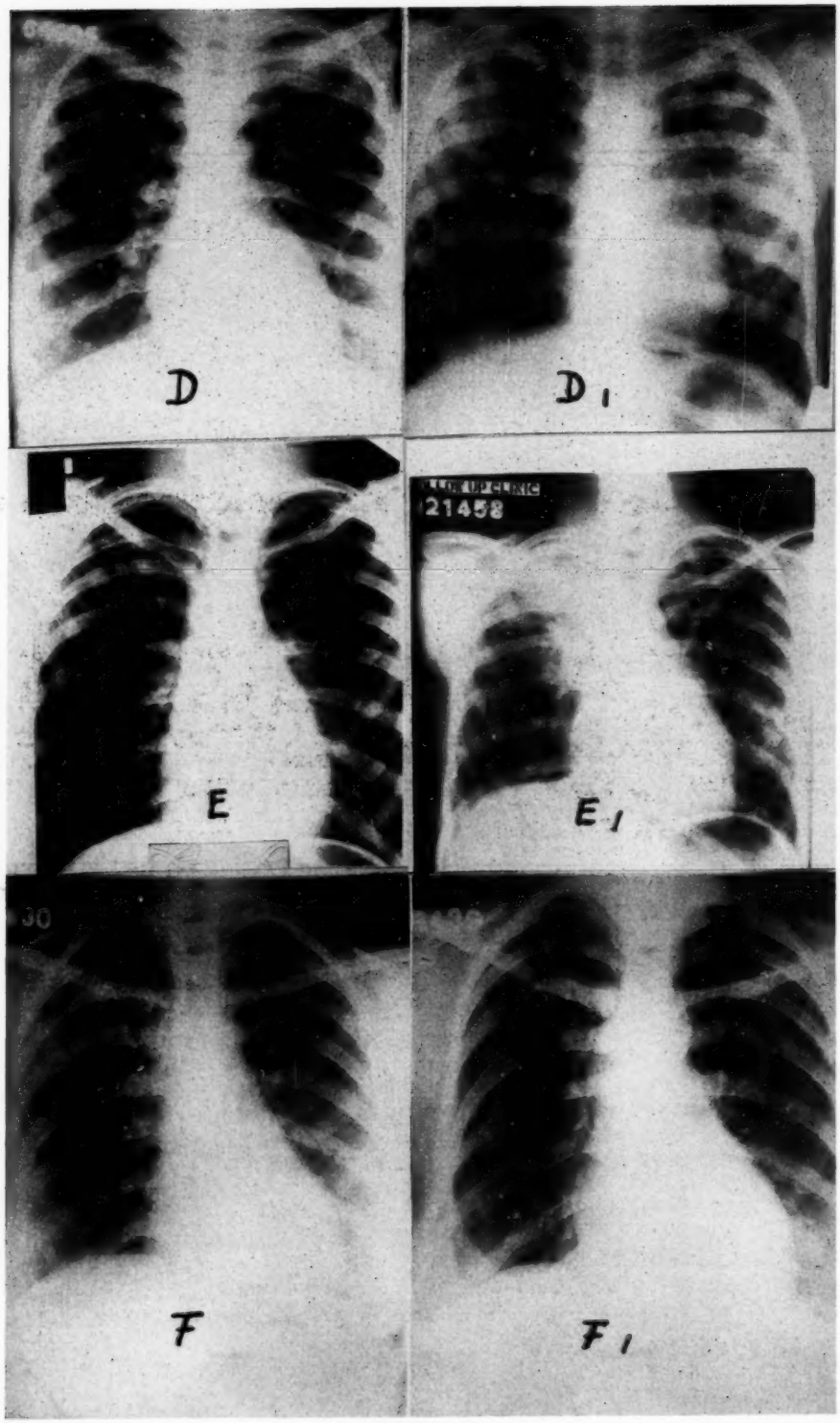

PLATE 2

3. Of 65 boys who still remain symptom free, 33.8 per cent show progressive changes by X-ray. Of 127 girls who are still without symptoms, 41.7 per cent show progressive changes on serial films.

4. Of the whole group, 19.3 per cent have developed cavities, 15.6 per cent boys and 21.0 per cent girls.

5. Of the group who had no sputum or negative sputum at the time of the original diagnosis, 23.1 per cent have developed positive sputum in an average interval of 3.5 years after diagnosis.

6. Ninety-five girls and 27 boys have died from pulmonary tuberculosis; one boy died from another cause.

7. Of the boys, 74.5 per cent and of the girls, 68.3 per cent received sanatorium treatment.

PLATE 2

FIGS. D & D_1. Apical lesion, progressive. Case 4. J. E. Girl, fifteen years and seven months old, weight 120 pounds, height 62.5 inches. Five pounds above average. Asymptomatic. Initial film D: March, 1930. Mottled shadow left apex to second anterior rib. Calcified node in extreme apex. Calcified nodes in right hilum. July, 1930, in sanatorium, afebrile and gained in weight until early in 1931 when she began losing weight despite bed-rest. Toxic in May, 1931, with symptoms and positive sputum. Lesion to third left anterior rib with a cavity in first left anterior interspace. In July, 1931, haemoptysis. August, 1931, spread in right. Serial film D_1: May, 1932. Bilateral coarse and fine mottling with large cavity in left first and second anterior interspaces. Died in July, 1932. Duration of life, two years and four months.

FIGS. E & E_1. Subclavicular lesion, progressive. Case 5. J. G. Girl, eleven years and eight months old, weight 68 pounds, height 57.5 inches. Fifteen per cent plus below average. Asymptomatic. Initial film E: April, 1931. Fine mottled shadow first and second right anterior interspaces. Calcified primary complex right hilum and along ninth posterior rib. Serial film E_1: October, 1932. Right apex to third right anterior rib, mottling with cavity; trachea to right, slight atelectasis. Left: infiltration in apex with questionable small cavity and fine mottled shadows in second, third and fourth left anterior interspaces. From December, 1932 to May, 1936 in sanatorium, gained to 99 pounds, always asymptomatic, but râles present in right. In July, 1934, right pneumothorax without result. Phrenicectomy in August, 1934. May 19, 1936, right thoracoplasty as left lesion retrogressed. Died on May 23, 1936. Duration of life, five years. (Note: This girl was under observation since eight years of age in 1928 for calcified primary complex.)

FIGS. F & F_1. Subclavicular lesion, retrogressive. Case 6. W. A. Girl, fifteen years and five months old, weight 102 pounds, height 63 inches. Ten per cent below average. Asymptomatic. Râles right top. Initial film F: June, 1929. Homogeneous shadow first and second right anterior interspaces. Calcified node in left apex and along ninth left posterior rib. From 1929 to 1933 in sanatorium off and on, always asymptomatic and sputum never positive. Lesion showed steady retrogressive change to calcification and fibrosis. Discharged as quiescent in April, 1933. Serial film F_1: May, 1936. Calcified node in right apex, fine strand in right apex and first right anterior interspace. Calcified nodes along right tracheobronchial region. Calcified node in left apex and along left ninth posterior rib. Well.

8. Of the 141 living boys, 69 are still under treatment at sanatoria; 19 are unimproved at home, and 53 (37.6 per cent) are well. Of the 272 living girls, 97 are still under sanatorium treatment, 53 are unimproved at home and 122 (44.8 per cent) are well.

MORTALITY

The case fatality of a chronic disease such as pulmonary tuberculosis cannot be expressed simply by stating the number of deaths as a percentage of the whole number, as it is correct to do for an acute disease, for example, lobar pneumonia. To determine the rate of mortality for pulmonary tuberculosis, a disease which must be observed for a long period of time, it is necessary to consider in the first place that the number available for calculations becomes less and less as time goes

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PLATE 3

FIGS. G & G_1. Retrogressive lesion. Case 7. P. K. Boy, eight years and seven months old, weight 55.5 pounds, height 50 inches. Six pounds below average. Always delicate, "bronchitis" since birth. Initial film G: January, 1932. Homogeneous shadow in right apex to first anterior rib. No visible calcification. From March, 1932 to August, 1933 always afebrile and asymptomatic. Steady retrogressive change to late in 1933 when definite calcified nodes replaced the shadow seen in 1932. Lesion has remained stable to January, 1937, serial film G_1. In school. Weight 79 pounds, height 59 inches. Ten per cent below average.

FIGS. H & H_1. Retrogressive lesion. Case 8. K. J. Girl, fifteen years and two months old, weight 115.5 pounds, height 66.5 inches. Ten per cent below average. Asymptomatic. Initial film H: May, 1931. Coarse mottled shadow right apex to third anterior rib. Irregular shadow left first and second anterior interspaces. Calcified nodes not visible. Highlight along fourth anterior rib left is blood vessel. From August, 1931 to February, 1936 in sanatorium. Slow steady retrogression. Steady gain in weight to 131 pounds. Always asymptomatic Serial film H_1: February, 1936. Strands with calcified spots in first right anterior interspace. Calcification in right hilum. Strands with calcified spots in left apex and first and second anterior interspaces. Is well and working.

FIGS. I & I_1. Retrogressive lesion. Case 9. S. D. A. Girl, eleven years and four months old, weight 56 pounds, height 53 inches. Fifteen per cent below average. "Bronchitis" since birth. Râles in right apex. Initial film I: February, 1932. Homogeneous shadow right apex to beyond second anterior rib, one or two small ring shadows in first right anterior interspace. No calcification visible. From April, 1932 to January, 1935 in sanatorium. Symptomatic with fever. Sputum positive once in April, 1932 and again May, 1933. Shadow began to show retrogressive changes in April, 1932 and became stabilized by 1935. Serial film I_1: January, 1937. Stringy shadow in right apex. Heavy comet-like streak is the vena azygos usually seen in this position. Few strands in second right anterior interspace. Calcified node in right hilum. (Obliteration of left costophrenic angle was produced in reduction.) In school. Weight 101 pounds, height 61 inches. Ten per cent below average. Differential diagnosis: atelectasis and foreign body, upper lobe bronchiectasis, interlobar pleural effusion, and lung abscess.

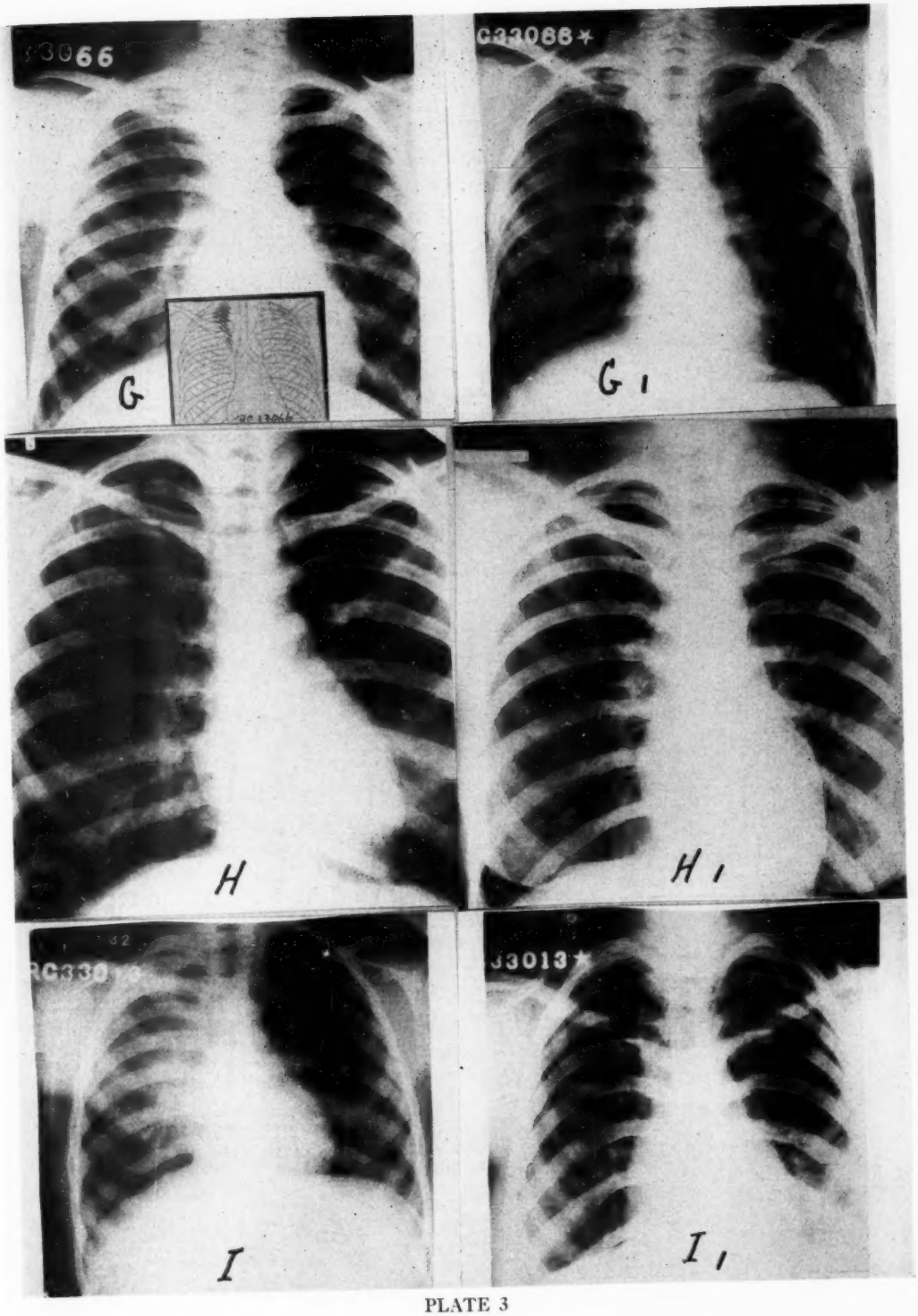

PLATE 3

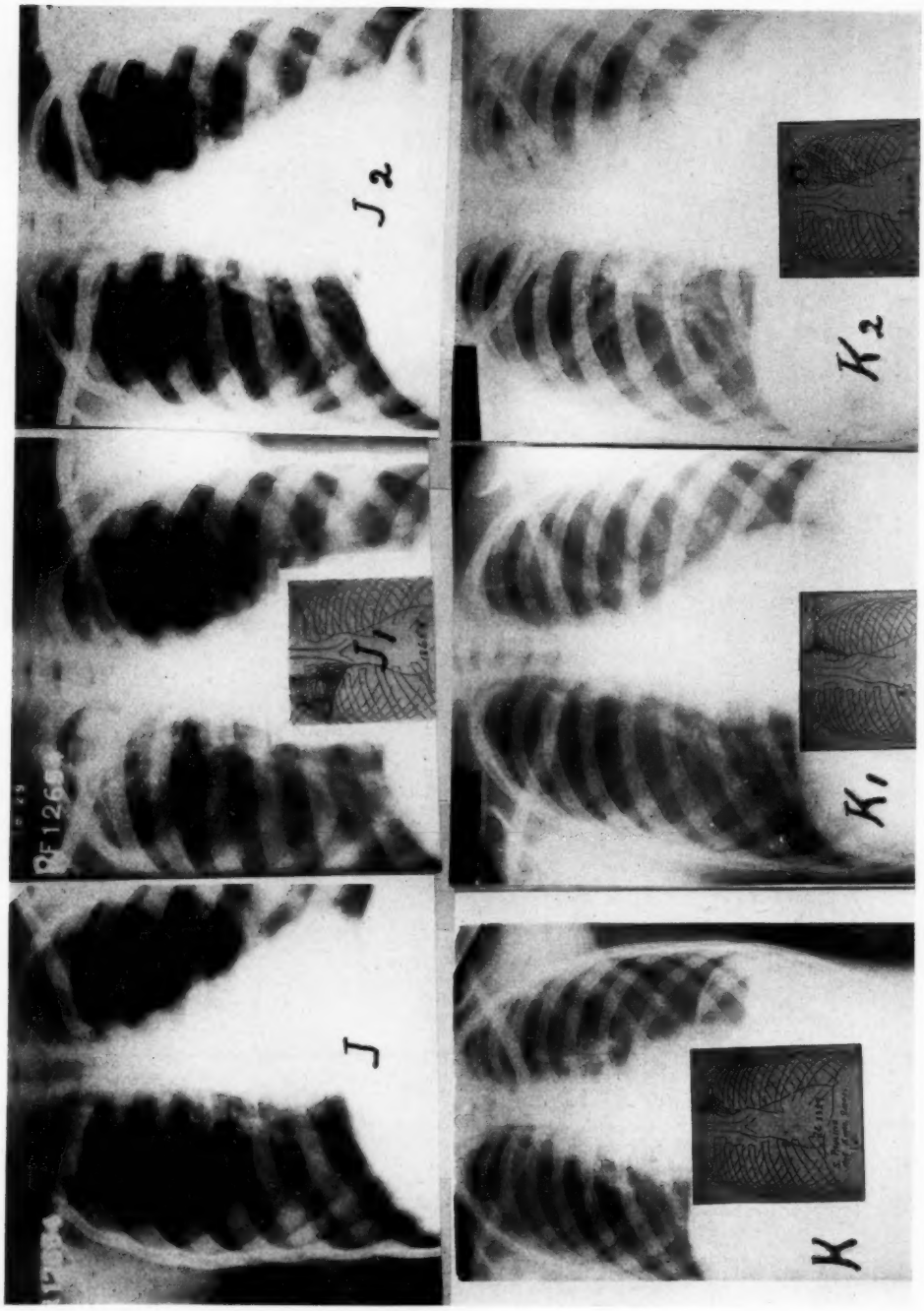

PLATE 4

on, and, in the second place, that the patients came under observation in small numbers year by year and some are observed longer than others. For this reason, the computations must be made step by step from year to year by actuarial methods. Mortality obtained in this way is spoken of as the cumulative mortality. To obtain a stable rate, the actuarial method requires a large number of cases, the larger the number, the more stable the rate. In the group under discussion, the number on which the mortality rate is based in each year is too small to give stable rates. However, the rates for the first year, the first five years, and the whole ten-year period, are significant and agree with actual clinical experience. The mortality is based on white children only.

The significant fact in table 3 is the delay in the cumulative mortality. The ultimate outcome in tuberculosis is uncertain during at least ten years of observation, especially for minimal lesions. For boys, the mortality at the end of five years' observation is 6.5 times that of the first year, and at ten years, 12.8 times that of the first year. For girls the five year mortality is 7.4 times, and the ten year mortality is 17.4

PLATE 4

FIGS. J, J_1 & J_2. Progressive, then retrogressive lesion. Case 10. M. J. Girl, eleven years and nine months old, weight 78 pounds, height 57.6 inches. Five per cent below average. Asymptomatic. Initial film J: March, 1927. Coarse mottled shadow in upper right mediastinum, extending into first and second right anterior interspaces. No calcification. December, 1929, age thirteen years and seven months, weight 100 pounds. In school with "head cold," râles right top. Serial film J_1: Homogeneous shadow with well defined lower margin and ring shadow in first right anterior interspace. From March, 1930 to February, 1933 asymptomatic. In State Sanatorium. Admission film (March, 1930) showed considerable clearing over that in December, 1929. Cavity not definitely visible. Gained weight to 130 pounds. Râles disappeared in November, 1932. February, 1933 apparently arrested. In 1936 well and working. Serial film J_2: Discrete, sharp shadows, calcified, are all that remains in place of the extensive lesion seen in serial film J, December, 1929.

FIGS. K, K_1 & K_2. Retrogressive, then progressive lesion. Case 11. S. P. Girl, five years and nine months old, weight 37.5 pounds, height 42.5 inches. Average weight. Asymptomatic. Initial film K: February, 1930. Homogeneous shadow left apex. No visible calcium. From 1930 to 1934 retrogressive changes with one or two calcified spots in the centre of lesion; this is not complete, however, since hazy shadow remains about the calcified core. Serial film K_1: June, 1934 to May, 1935, slight spread to first left anterior interspace. Weight stationary at 70 pounds. Height stationary at 53 inches. Asymptomatic. Lesion continued to spread slowly though weight increased. Serial film K_2: May, 1937. Fine to coarse mottled shadow throughout left lung field. Small cavity left apex. (Fine mottled shadow in second right anterior interspace.) Age thirteen years, weight 94 pounds, height 59 inches. Average weight 92 pounds. Is symptomatic.

times that of the first year. The mortality was also calculated for the special groups shown below with the following results:

Positive sputum cases, cavity cases and cases showing X-ray progression give a consistently high mortality with or without treatment.

The mortality rate for open cases is 7.4 per cent a year for boys and 12.5 per cent for girls.

The rate for cavity cases is 8.4 per cent a year for boys and 14.0 per cent for girls.

The rate for progressive lesions according to X-ray observation is 6.7 per cent a year for boys and 11.4 per cent for girls.

TABLE 3

*Cumulative mortality from pulmonary tuberculosis during various time periods after discovery of disease in 169 boys and 367 girls, according to age groups in years when diagnosis was first made**

AGE GROUP	NUMBER OF CHILDREN		DEATHS FROM PULMONARY TUBERCULOSIS											
			Within one year				Within five years				Within ten years			
	M	F	M	Per cent	F	Per cent	M	Per cent	F	Per cent	M	Per cent	F	Per cent
years														
0–9	8	11	0	0	0	0	1	13.3	0	0	2	56.6	0	0
10–14	64	144	0	0	2	1.4	8	16.4	30	28.7	11	36.4	45	67.4
15–23	97	212	5	5.4	11	5.5	14	21.5	40	26.7	14	21.5	50	64.6
Total.....	169	367	5	3.0	13	3.7	23	19.5	70	27.3	27	38.8	95	64.4

* Basic table showing steps in calculation from year to year is not given. The method used is the common life experience and mortality tables used in actuarial computation.

Boys with positive sputum have 3 times the mortality of closed cases, girls with positive sputum have over 3.5 times the mortality of closed cases.

There was no significant difference in mortality between contact and noncontact groups (contact boys, 3.8 per cent a year; noncontact boys, 4.5 per cent a year; contact girls, 6.9 per cent a year; noncontact girls, 5.6 per cent a year).

Pulmonary lesions accompanied or preceded by calcified tracheobronchial nodes show a slightly, but not significantly, lower mortality for boys (boys with calcified nodes, 3.8 per cent a year, boys without such nodes, 4.1 per cent a year). For girls, the mortality of pulmonary lesions accompanied or preceded by calcified nodes was 5.5 per cent a year, against 9.0 per cent a year when calcified nodes were absent in the

film. This fact would suggest a lesser resistance to the inroads of the disease in the group of girls without calcified nodes.

DURATION OF LIFE

Table 2 shows that the death rate is directly proportional to the extent of the lesion at the time of diagnosis. It appears further that the duration of life in morbid cases has an inverse relationship to the age at diagnosis as well as to the extent of the lesion. For the age group five to nine years, the duration of life was 6 years; for the age group ten to fourteen years, 5 years; for the age group fifteen or more years, 3 years. Does this mean that the lesions when found were more advanced in the older age groups, or does a lesion spread more rapidly when acquired in mid or late puberty? The data presented earlier (table 1) would indicate that the lesions were more advanced in the older age groups. This fact, however, is not the entire explanation. Age *per se* is also a factor to be reckoned with. For it was found that for lesions of similar extent the duration of life is shorter, the older the patient at the time of diagnosis. For minimal lesions, the duration of life for the age group five to nine years was 6 years; for the age group ten to fourteen years, 5.3 years; for the age group fifteen or more years, 4.1 years. For advanced lesions, the duration of life for the age group ten to fourteen years was 3.6 years; and for the age group fifteen or more years, 2.3 years. It is noteworthy that the sexes show very little difference in the duration of life in morbid cases.

SUMMARY

A group of 536 children with pulmonary tuberculosis, the majority in the second decade of life, diagnosed by X-ray in the great majority of instances, was observed carefully an average of four person years. The course of the early, minimal, asymptomatic lesions was traced and the behavior of the individual lesions was discussed. It was shown that within the period of observation two-thirds of the lesions have progressed according to X-ray observation, when symptoms, cavities and positive sputum developed and their rate of development per hundred person years was calculated. Roentgenograms were presented to illustrate the courses of the early lesions in the spreading and retrogressive phases. The cumulative mortality for such a group was calculated for the first year, the first five years and the entire period of observation.

CONCLUSIONS

Tuberculous disseminations or reinfections in the second decade of life begin as minimal lesions early in the decade, spread slowly in the majority of instances by contiguity as time goes on, and show no symptoms or at most imperceptible symptoms at first. With the arrival of mid or late puberty, the lesions have advanced to such an extent as to give symptoms referable to the chest or toxic symptoms. The diagnosis is usually made with the advent of symptoms, unless the lesions are discovered earlier by routine X-ray examination of tuberculin-positive children. In the great majority of instances, these lesions will be found in the apices. These asymptomatic X-ray lesions, once they have been differentiated from similar nonspecific lesions which may mimic them, should be regarded as of grave import. Asymptomatic lesions, when soft in appearance, show in general two distinct phases of behavior according to serial X-ray films; one type shows a tendency to spread, the other to retrogress. This behavior, unfortunately, cannot be foretold by the X-ray appearance of the initial lesion. The progressive lesions may spread slowly or rapidly, and will kill the great majority of patients within ten years, the duration of life depending inversely upon the extent of the lesion and the age at the time of diagnosis. The retrogressive type of lesions tends to subside during a longer or shorter interval of time, and the patient will survive puberty, the critical period for this group of patients.

The subclavicular or infraclavicular lesions show the greatest proportion of spread and the highest cavity rate for lesions of minimal extent. Toxic symptoms are of prognostic rather than diagnostic significance in this age group.

Although the incidence of pulmonary tuberculosis is twice as high in girls of this age, the subsequent course of the disease and the case fatality is essentially the same as in boys.

I wish to thank the Clinic Clerks, Miss Riordan, Miss Block, Miss Marquis and Miss Morrissey, for their help in the preparation of this paper; Miss Hamblen, our Statistician, for her work in checking the tables and estimating their significance; Dr. H. D. Chadwick, Dr. A. S. Pope and Dr. Roy Morgan, for their patience and kindness which made this study possible.

PULMONARY TUBERCULOSIS IN THE SECOND DECADE OF LIFE[1]

II. Its Treatment and Prognosis

DAVID ZACKS

In a previous communication (1) the development and fatality of pulmonary tuberculosis in the second decade of life were discussed. In this paper will be considered its treatment and its prognosis as measured by X-ray observation. The study is based on 536 children with pulmonary tuberculosis who were followed an average of four years. The longest period of observation was twelve years, the shortest was one year. The clinical status of the treated and untreated boys and girls at the end of the follow-up period is given in table 1.

The most pertinent observation in table 1 is the slightly greater mortality in the treated than in the untreated boys and girls. The treated boys give a mortality rate of 4.2 per cent a year, the untreated 3.2 per cent a year. The mortality for the treated girls is 7.1 per cent, the untreated 5 per cent. This result can be explained only on the basis of selection as the more advanced cases were naturally the first to accept treatment.

TREATMENT

Treatment for pulmonary tuberculosis might be expected to do two things—it might at least prolong the life of the patient or it might at most assist nature to arrest the progress of the disease. An accurate appraisal of the result of any method of treatment must be based on not less than ten years of observation. In Massachusetts, until 1932, treatment for children in the second decade of life was bed-rest at a sanatorium. The rest treatment, until 1927, was of short duration, or in febrile patients as long as the fever continued. Beginning in 1927, one year of bed-rest was routine treatment for all children with pulmonary infiltrations regardless of extent.

Treatment by bed-rest alone: Patients with pulmonary tuberculosis in

[1] From the Massachusetts Department of Public Health, Boston, Massachusetts.

TABLE 1

Status of 169 boys and 367 girls at the end of the follow-up period after 4 mean person years of observation

SEX	TREATED		UNTREATED		TOTAL	
	M	F	M	F	M	F
Number of persons	126*	252†	43	115	169	367
Per cent of persons	74.5	68.7	25.4	31.3	100.0	100.0
Treatment years	262.0	489				
Person years observation	517	1,033	157.5	436.5	674.5	1,469.5
Mean person years	4.1	4.1	3.7	3.8	4.0	4.0
Result at the end of the follow-up period						
Number dead	22	73	5	22	27	95
Per cent dead	17.5	28.9	11.6	19.1	16.0	25.9
Death per 100 person years	4.2	7.1	3.2	5.0	4.0	6.5
Number living	104	179	37‡	93	141‡	272
Per cent living	82.5	71.0	86.0	80.9	83.4	74.1
Number at sanatorium	65	84	0	0	65	84
Per cent at sanatorium	62.5	46.9	0	0	46.1	30.9
Number unimproved	9	16	10	37	19	53
Per cent unimproved	8.6	8.9	27.0	39.8	13.5	19.5
Number well and reported well	27	73	26	49	53	122
Per cent well and reported well	26.0	40.8	70.3	52.7	37.6	44.8
Number with home treatment	0	3	1	7	1	10
Per cent with home treatment	0	1.7	2.7	7.5	0.7	3.7
Number O.P.D. pneumothorax	3	3	0	0	3	3
Per cent O.P.D. pneumothorax	2.9	1.7	0	0	2.1	1.1

* Boys:
55 Sanatorium only
71 Sanatorium with surgical procedure
46 Pneumothorax only
4 Pneumothorax with thoracoplasty (1 also phrenicectomy)
4 Pneumothorax with pneumonolysis
6 Pneumothorax with phrenicectomy
8 Phrenicectomy only
3 Thoracoplasty only (2 had phrenicectomy).

† Girls:
132 Sanatorium only
120 Sanatorium with surgical procedure
75 Pneumothorax only
6 Pneumothorax with thoracoplasty (3 phrenicectomy)
10 Pneumothorax with pneumonolysis (1 phrenicectomy)
17 Pneumothorax with phrenicectomy
11 Phrenicectomy only
1 Thoracoplasty only (1 phrenicectomy).

‡ One (1) boy died of other causes.

the advanced or moderately advanced stages, according to the accepted classification, were naturally the first to accept sanatorium treatment. When the child was objectively ill there was no question as to the necessity for treatment either by the child's family or by the family physician. Unfortunately, bed-rest alone for shorter or longer periods, judged by the ten-year standard, has failed utterly to influence the course of the disease. This statement is not only true for the advanced positive sputum cases, but is also true for minimal cases that progress according to X-ray observation.

Morgan (2) wrote in 1934 that the vast majority of positive sputum cases will be lost even if given prolonged bed-rest. Klare (3) in Germany,

TABLE 2

Mortality rates for treated and untreated special groups

	NUMBER		MEAN PERSON YEARS		PER CENT DEAD		DEATH RATE PER 100 PER YEAR	
	Boys	Girls	Boys	Girls	Boys	Girls	Boys	Girls
Total:								
Treated	126	252	4.1	4.1	17.5	28.9	4.2	7.1
Untreated	43	115	3.7	3.8	11.6	19.1	3.2	5.0
Open cases:								
Treated	50	117	3.8	3.9	28.0	47.0	7.4	12.0
Untreated	0	10	0	3.6	0	70.0	0	19.5
Cavity cases:								
Treated	40	101	3.6	3.9	30.0	52.5	8.3	13.4
Untreated	3	18	3.2	3.9	33.3	66.7	10.5	17.1
X-ray progressive lesions:								
Treated	95	166	3.7	3.8	23.2	43.9	6.2	11.6
Untreated	16	63	2.8	3.2	31.2	34.9	11.1	10.8

reporting in 1936 on a series of 502 open cases in children and youths followed ten years or more, found a mortality of 95.5 per cent with 4.5 per cent able to work. This mortality was the same for boys and girls. Cochrane (4), in England, in 1935 reported a mortality of 74.9 per cent for boys and 71.3 per cent for girls in sanatorium treated open cases that were discharged during the years 1922 to 1929. Our experience with open cases, with cavity cases and with minimal lesions that showed progression by X-ray under observation is given in table 2.

This table shows a striking mortality for the treated as well as the untreated groups. In the open cases the treated boys gave a mortality of 7.4 per cent a year and the girls 12 per cent a year. The cavity cases

showed a mortality of 8.3 per cent a year for the treated boys and 13.4 per cent a year for the treated girls. Lesions that showed progression by X-ray are not far behind with a mortality of 6.2 per cent a year for the treated boys and 11.6 per cent a year for the treated girls. Of the 50 treated boys with open lesions, 31 had pneumothorax (2 with pneumonolysis), 4 had thoracoplasty (2 with phrenic interruption) and 8 had phrenicectomy only. Of the 117 treated girls with positive sputum, 72 had pneumothorax (4 with pneumonolysis, 1 also with phrenic interruption), 5 had thoracoplasty (3 with phrenic interruption), and 19 had phrenicectomy only. Details of treatment for cavity cases are given in table 5.

Bed treatment in progressive lesions: In our experience, bed-rest alone in a sanatorium does not modify the course of spreading tuberculous lesions to an appreciable degree and does not reduce the mortality for these lesions. This statement is supported by the data in table 3.

In this table, treatment refers to all forms of treatment, namely, bed-rest at sanatorium, pneumothorax and other surgical procedures. Early treatment refers to treatment instituted within one year of diagnosis. Later treatment means active treatment begun one or more years after diagnosis. For the purpose of this analysis 158 children who received no treatment were combined with 114 who received later treatment. No difference was observed in the early treated group as against the untreated or later treated group in the proportion of spread. The group with early treatment shows a slightly better but not significantly better mortality than the untreated group. The group that showed spread by X-ray despite early treatment had a mortality of 32.8 per cent after four years of observation, against a mortality of 38.9 per cent for the non-treated group, not a significant difference.

The significance of asymptomatic minimal lesions was not fully and generally appreciated, even by tuberculosis specialists until comparatively recently, paradoxical as this may sound. This ignorance was general and was due to a lack of sufficient experience with these lesions and consequently an unwillingness to make a diagnosis, to say nothing of recommending treatment on X-ray evidence alone. For many years the cry had been, "Find the early cases!" When a method had been elaborated whereby the really early lesions were discovered by the use of the tuberculin test and the X-raying of reactors, we did not know how to treat these lesions, or indeed, whether treatment was necessary. In the absence of symptoms and signs, these early X-ray lesions were pre-

maturely labeled "latent," a term which was generally taken to mean "inactive" or "healed." It was said that we had better wait until the lesions had become "manifest," that is, had physical signs such as râles, and symptoms referable to the chest. It has required time to demonstrate the potential danger of these innocent and insignificant looking lesions.

TABLE 3

X-ray at the end of the follow-up period for 536 pulmonary cases according to treatment after 2,144 person years of observation

RELATION OF TREATMENT TO END RESULT BY X-RAY	TOTAL NUMBER, 536 MEAN YEARS, 4.0		X-RAY RESULT AT THE END OF THE FOLLOW-UP PERIOD							
			Progressed 340 (63.4%)		Retrogressed 129 (24.1%)		Stationary 37 (6.9%)		Unknown 30 (5.6%)	
	With early treatment	Without or with later treatment	With early treatment	Without or with later treatment	With early treatment	Without or with later treatment	With early treatment	Without or with later treatment	With early treatment	Without or with later treatment
Number of children	264	272	168	172	74	55	19	18	3	37
Percentage of change			63.6	63.2	28.0	20.2	7.2	6.6	1.1	9.9
Per cent dead after 4 mean years	20.8	24.6	32.8	38.9	0	0	0	0	0	0
Boys										
Total number boys 169 Mean years 4.0	88	81	62	49	20	16	5	5	1	11
Percentage of change			70.5	60.5	22.7	19.7	5.6	6.2	1.1	13.6
Per cent dead after 4 mean years	14.6	17.3	21.0	28.6	0	0	0	0	0	0
Girls										
Total number girls 367 Mean years 4.0	176	191	106	123	54	39	14	13	2	16
Percentage of change			60.2	64.4	30.7	20.4	8.0	6.8	1.1	8.4
Per cent dead after 4 mean years	23.9	27.7	39.6	43.1	0	0	0	0	0	0

Nevertheless, some of these early lesions were hospitalized after a great deal of effort in persuading the family physicians and indeed the tuberculosis specialists that treatment was indicated. The treatment consisted of short periods of bed-rest and, when this failed, to prevent readmissions a longer period of bed-rest was given without any better results. Time and again, when soft lesions remained stationary, as

they will do for some time, the patients were discharged as "arrested" because there were no symptoms and the weight and general condition had improved under bed-rest. The patients, however, usually returned with the lesion more extensive than before. The lesions that retrogressed as shown by X-ray did well with bed-rest, as they usually will without any treatment at all. The lesions that spread continued to spread despite periods of bed treatment. Morgan (2) in 1934 stated, "The end results in the incipient and moderately advanced cases seem about the same (in mortality) although the incipient did better for a time. This can probably be explained by the fact that we did not take these incipient cases seriously enough and discharged them too early." (See table 3.) Bed treatment was in vogue at Westfield Sanatorium until 1932 when pneumothorax treatment came into more general use.

Sanatorium plus pneumothorax treatment: Pneumothorax treatment judged over a period of ten years has not benefited the course of the disease in the advanced stages to any appreciable extent. Klare (3) reports a mortality after ten years of 90.9 per cent with 9.1 per cent able to work. His mortality was the same for boys as for girls. Our experience with collapse therapy according to the topography of the lesions is given in table 4.

The most that can be said, perhaps, for this form of treatment in advanced bilateral lesions is that it tends to prolong life. The mortality for all bilateral lesions in girls is 12.9 per cent a year for bed treatment only, and 11.2 per cent a year for collapse therapy. For boys with bilateral lesions, the mortality for sanatorium treatment is 8.8 per cent a year and for pneumothorax 7.1 per cent a year. A better result is indicated for all unilateral lesions in girls, especially for the subclavicular and minimal apical lesions. The result with collapse therapy for unilateral lesions in boys is rather significantly better. Table 4, moreover, is not offered as a final answer to the benefit of really early collapse on minimal lesions. The lesions given in this table are the lesions as found at the time of diagnosis, but the collapse in the majority of instances was not applied soon after the diagnosis was made. This procedure is of more recent development. The tendency in most instances had been to treat first by bed-rest alone and then, if a definite spread occurred, by collapse. The table does show what to expect from pneumothorax for advanced lesions and lesions discovered early but allowed to progress too far before collapse is instituted.

Our experience with collapse therapy in cavity cases is given in table

TABLE 4

Comparison in end results between sanatorium treatment only and sanatorium treatment plus pneumothorax treatment, by sex and topography of X-ray lesions, in mean years of observation

TOPOGRAPHY OF X-RAY LESIONS AT TIME OF DIAGNOSIS	BOYS								GIRLS							
	Sanatorium only				Sanatorium + pneumothorax				Sanatorium only				Sanatorium + pneumothorax			
	Number	Mean years observation	Per cent dead	Death rate per 100 per year	Number	Mean years observation	Per cent dead	Death rate per 100 per year	Number	Mean years observation	Per cent dead	Death rate per 100 per year	Number	Mean years observation	Per cent dead	Death rate per 100 per year
Subclavicular Lesions	2	2.0	0	0	11	3.7	0	0	13	4.1	38.5	9.3	16	3.6	12.5	3.4
Unilateral:																
Apex above clavicle	11	5.7	9.1	1.6	12	4.3	0	0	31	4.4	16.1	3.7	18	3.9	11.1	2.9
Apex to second anterior rib	10	5.0	40.0	8.0	7	4.9	0	0	25	4.9	12.0	2.5	19	4.7	15.8	3.3
Apex to beyond second anterior rib	3	6.8	33.3	4.9	9	2.9	11.1	3.8	13	4.6	61.5	13.4	13	4.0	30.8	7.6
Unilateral with cavity	2	3.0	50.0	16.7	2	2.0	0	0	6	4.0	33.3	8.3	13	2.2	15.4	7.0
All Unilateral Lesions	26	5.3	26.9	5.0	30	3.9	3.3	0.9	75	4.5	24.0	5.3	63	3.8	17.5	4.6
Bilateral:																
Apices above clavicles	13	4.7	7.7	1.6	5	5.3	0	0	13	6.4	15.4	2.4	5	3.7	40.0	10.8
Apices to second anterior ribs	6	5.5	50.0	9.1	4	4.0	25.0	6.3	9	4.1	44.4	11.0	5	5.9	40.0	6.8
Apices to beyond second anterior ribs	3	2.8	100.0	35.3	2	1.5	50.0	33.3	12	3.0	75.0	25.0	4	4.0	50.0	12.5
Bilateral with cavity	5	2.1	60.0	28.6	7	1.5	28.6	19.1	9	1.6	77.8	48.3	15	2.9	40.0	13.8
All Bilateral Lesions	27	4.2	37.0	8.8	18	3.1	22.2	7.1	43	4.0	51.2	12.9	29	3.7	41.4	11.2
Total Lesions	55	4.7	30.9	6.6	59*	3.6	8.5	2.3	131†	4.3	34.4	8.0	108	3.8	23.1	6.2

* One boy not included because location and extent of original X-ray lesion unknown.

† One girl not included because location and extent of original X-ray lesion unknown.

5. The mortality for the cavity group as a whole is consistently very high, but for the same period of observation collapse therapy gives an immediately better result. The boys with collapse therapy have one-third the mortality, the girls one-half the mortality of bed-rest only. Of the 19 boys with bed treatment, 3 had phrenicectomy, 1 had thoracoplasty and 2 had phrenicectomy and thoracoplasty. Of the 45 girls with bed treatment, 3 had phrenicectomy and 1 had phrenicectomy and thoracoplasty. Of the 21 boys with pneumothorax, 3 also had phrenicectomy, 3 had thoracoplasty (1 also had a phrenic interruption),

TABLE 5

End result of cavity cases

Sex	Boys			Girls			Boys	Girls
Method of treatment	Bed only	Bed with pneumothorax	Total treated	Bed only	Bed with pneumothorax	Total treated	Untreated	
Number	19	21	40	45	56	101	3	18
Person years	70.5	74.5	145	181.5	213.0	394.5	9.5	70.0
Mean person years	3.7	3.6	3.6	4.0	3.8	3.9	3.2	3.9
Result at end of follow-up period								
Number dead	9	3	12	33	20	53	1	12
Per cent dead	47.4	14.3	30.0	73.3	35.7	52.5	33.3	66.7
Deaths per 100 per year	12.8	4.0	8.3	18.2	9.4	13.4	10.5	17.1
Number living	10	18	28	12	36	48	2	6
At sanatoria	7	16	23	6	30	36		
At home unimproved	1		1	3	3	6	2	6
Well and reported well	2	1	3	3	2	5		
O.P.D. pneumothorax		1	1		1	1		

2 had pneumonolysis. Of the 56 girls with pneumothorax, 7 had phrenicectomy, 4 had thoracoplasty (2 also had a phrenic interruption), 3 had pneumonolysis and 1 had pneumonolysis and phrenicectomy. The great majority of the surviving boys and girls are still under treatment, however, with the ultimate outcome still problematical. It is noteworthy that only 8 patients out of a total of 162 are well.

The real question as to whether an early attack by collapse therapy on an early lesion will actually prevent the spread of the lesion and arrest the course of the disease remains unanswered. This problem is now being studied. Another five years will be necessary before a preliminary

report can be made. We need a standard by which to judge adequately this method of treatment. Some lesions we have seen to retrogress without treatment, others have progressed despite treatment. We must first ascertain whether we are collapsing the progressive type of lesion and then we must find the optimum period for collapsing a lesion. These are all questions for the future.

Thoracoplasty: In this series, there were 14 thoracoplasties of various stages (7 boys and 7 girls). Of the total number, 10 had preliminary pneumothorax of long or short duration, and of the remaining 4, 3 had preliminary phrenics. There was one operative death among the girls. Of the boys, after 6.5 person years of observation (three person years after the surgical operation) 4 are still in sanatoria doing well and 3 have been discharged and are well. Of the 6 living girls after 6.5 person years of observation (approximately two person years after the surgical operation) 3 cases are still at sanatoria, 2 in fair condition, 3 have been discharged and are well.

As indicated, the result with thoracoplasty on the whole, although the number is small, is better than with pneumothorax, but this is probably largely a matter of selection. Nevertheless, in properly selected cases, thoracoplasty should not be deferred on account of the age of the patient, granted that the case selection for this procedure is definitely limited in this age group.

SUGGESTED PROCEDURE WITH COLLAPSE THERAPY

A hard and fast rule cannot be given as to procedure with pneumothorax treatment in the individual case. The following general suggestions may be found helpful.

In the age group five to nine years, chronic subclavicular infiltrations should be treated by bed-rest alone.

In older age groups, attack immediately cavity cases and apical lesions beyond the second anterior ribs. For subclavicular processes, allow a month or two in bed for observation by frequent serial films to determine whether the lesion shows definite retrogressive changes. If definite retrogressive changes do not occur, if the lesions remain stationary or show a tendency to spread no matter how slight, attack at once. An exception to this rule is perihilar or peritracheal infiltrates when observed during their spreading phase (formation of secondary infiltrates) which should not be collapsed immediately as these lesions will probably undergo spontaneous retrogressive changes. Apical lesions not greater in

extent downward than the second anterior ribs should be given a period of three to six months' observation in a sanatorium by serial films. If the lesions do not show a tendency to retrogress at the end of the period, then attack by pneumothorax. If adhesions hamper a good collapse, these should be surgically severed without waiting too long and the pneumonolysis should be done as thoroughly as possible to give the desired result. Pneumothorax should not be carried on too long for extensively adherent apical lesions that cannot be severed by pneumonolysis, as thoracoplasty is a much better procedure for these cases and will often avoid purulent exudates.

PROGNOSIS FROM X-RAY POINT OF VIEW

The prognosis is good for sub- or infraclavicular infiltrative lesions in the first decade of life. These lesions as a whole behave like primary infiltrates in that they subside sooner or later, with or without treatment, and leave in place of the infiltrate residual calcified nodes or strand-like shadows or both. Soft apical infiltrations in the first decade of life are rare, but when they occur the prognosis is good if the lesions are unaccompanied by calcified tracheobronchial or parenchymal nodes. These children, however, should be followed after the lesions have subsided with yearly X-ray examinations through puberty. Apical lesions in the first decade of life accompanied or preceded by calcified nodes will behave like similar lesions in the second decade of life.

In the second decade of life the prognosis for soft early lesions is uncertain for at least ten years. In general it may be said that the prognosis is directly related to the extent of the apical lesions in relation to the anterior or posterior ribs. Extensive lesions beyond the second anterior ribs, cavity cases and sputum positive cases, have a poor prognosis. Recoveries may occur but they are rare. When advanced lesions are accompanied by toxic symptoms, the prognosis is usually immediately hopeless. In individual cases, more important than the extent of the lesion is the behavior noted by serial X-ray films. Lesions that progress, no matter how slowly, ultimately do poorly. Retrogressive lesions should be observed until they are definitely stabilized as indicated by fibrous strands, by calcification or by both. Subclavicular lesions that retrogress have a good prognosis—the reverse is true if they progress. A stationary lesion when soft in appearance, homogeneous or mottled, has an uncertain prognosis. It is best not to temporize too long with these lesions. A stationary lesion, definitely strand-like or stringy, with

or without calcified spots, has a good prognosis. This type of lesion should, however, be observed through puberty, particularly in girls.

CONCLUSIONS

1. Bed-rest alone in a sanatorium does not modify the course of spreading tuberculous lesions to an appreciable degree and does not reduce the mortality of these lesions.

2. Therapy, either bed-rest alone or bed-rest with pneumothorax, has not affected to any appreciable degree the mortality in advanced bilateral lesions, or lesions of minimal extent that are allowed to progress too far without early attack by collapse therapy. Collapse therapy in advanced unilateral lesions tends at least to prolong life and it may be demonstrated by further observation that it also reduces the mortality.

3. Some evidence has been presented which would seem to indicate that an early attack by collapse therapy may reduce the fatality rate of early asymptomatic lesions that show a tendency to spread. A final answer on this point cannot be given without at least five more years of observation.

4. In the second decade of life, the prognosis for soft early lesions is uncertain for at least ten years. In individual cases, most important in prognosis is the behavior of the lesion according to serial X-ray films. Lesions that progress ultimately do poorly—those that retrogress on the whole do well.

5. Retrogressive lesions should be observed by serial films until definite stabilization is evident either by calcification or strand-like fibrosis or both.

REFERENCES

(1) ZACKS, D.: Pulmonary tuberculosis in the second decade of life. I. Its development and fatality, Am. Rev. Tuberc., 1939, *39*, 683.

(2) MORGAN, R.: Certain aspects of pulmonary tuberculosis in children, Am. Rev. Tuberc., 1934, *29*, 577.

(3) KLARE, K.: Die Prognose der offenen Lungentuberkulose bei Kindern u. Jugendlichen, Beitr. z. Klin. d. Tuberk., 1936, *88*, 268.

(4) COCHRANE, E.: Course, complications, and prognosis of open pulmonary tuberculosis in children, Tubercle, 1935, *16*, 529.

DIABETES AND PULMONARY TUBERCULOSIS[1]

With Special Reference to the Lipid Content of Diabetic Lungs

HOWARD F. ROOT AND WALTER R. BLOOR

The peculiar relationship of diabetes and tuberculosis has been frequently studied since Avicenna (980–1027) commented upon phthisis as a frequent complication of diabetes. Lieutaud (1779), in a collection of several hundred autopsies, recorded cases of diabetes and phthisis; and John Rollo in 1798 described both clinical and postmortem records of cases of diabetes evidently complicated with pulmonary tuberculosis with cavitation. During the latter half of the nineteenth century the diabetic patient appeared doomed to die of pulmonary tuberculosis if he succeeded in escaping coma. Indeed, Bouchardat in 1883 stated in his text that at autopsy every case of diabetes had tubercles in the lungs. In the twentieth century, the association of the two diseases still occasions concern because of its great frequency, particularly in diabetic clinics of the great European cities where overcrowding and poverty insure the spread of tuberculosis. In Labbé's large hospital clinic pulmonary tuberculosis caused 40 per cent of the deaths in 1930, 1931 and 1932 (1), although in private cases the percentage is much more nearly like that of our own population. In any discussion of the frequency of pulmonary tuberculosis in diabetes, one must always bear in mind the effect of varying social conditions, types of population, the hospital from which the statistics are drawn and the type of diabetic treatment.

We have analyzed the records of tuberculosis occurring in 364 diabetic patients, of whom 119 are cases newly discovered, since 245 cases were described in 1934 (2). These 245 cases occurred among 9,592 true diabetics (among 11,023 glycosurics seen between 1898 and May 1, 1932) and 77 of these cases were discovered among 5,480 cases between May, 1932 and January 31, 1938. In the latter period naturally a large number of patients are included whose diabetes is still of short duration.

[1] From the George F. Baker Clinic, New England Deaconess Hospital, Boston, Massachusetts, and the School of Medicine and Dentistry, University of Rochester, Rochester, New York.

A better comparison would be the ratio of cases to the total number of years of diabetes lived by all patients during the two periods. From this series certain facts are outstanding:

1: The development of pulmonary tuberculosis in juvenile diabetics, or in patients whose diabetes began at or before the age of twenty, occurs more than twelve times as frequently as among all pupils in Massachusetts' grade and high schools. Forty per cent of deaths in diabetic children, with diabetes of more than ten years' duration, were due to tuberculosis.
2: Between 1923 and 1929 pulmonary tuberculosis developed in 8 per cent of 105 diabetic patients within three years of recovery from coma. Among 97 patients treated for coma between February, 1929 and November, 1932, 24 died of other causes within a year or two. Of the 73 patients remaining, 13 have developed tuberculosis within five years.
3: The incidence of pulmonary tuberculosis in adult diabetics does not show a decrease in rate corresponding with the general decrease in tuberculosis mortality in the community, for which fact explanation may be sought in the increasing longevity of the diabetic and prolongation of the period of exposure to tuberculosis.
4: In 83 per cent of the cases, the development of tuberculosis appeared to follow the onset of diabetes. In 2 per cent accurate data regarding times of onset are lacking. In 15 per cent earlier pulmonary tuberculosis had apparently been arrested (by sanatorium or other treatment) only to be reactivated after onset of diabetes.

INCIDENCE

To gain an impression of the incidence of tuberculosis in diabetic patients, one must consider autopsy as well as clinical statistics. Autopsy data are difficult to interpret (*1*) because, in such series, the effect of prolonged duration of diabetes has not been given sufficient weight. A review of the literature reveals the fact that, in a great majority of autopsies on diabetics, the duration of diabetes was less than five years. Nowadays, with modern insulin treatment, we expect the average young diabetic patient to live many years longer. Certainly, if diabetes does influence the development of tuberculosis, diabetes of one or two years' duration is too short an exposure to affect the patient's chance to develop tuberculosis. (*2*) In any large autopsy series, the frequency of association of tuberculosis with any chronic disease is much less than the incidence of tuberculosis in the group as a whole. Thus, we should compare the frequency of tuberculosis in diabetic patients with the frequency of tuberculosis in some other chronic disease, such as heart dis-

ease or carcinoma.[2] If such points are given consideration, then the frequency of pulmonary tuberculosis in diabetic patients at autopsy appears to be from two to four times as great as it is in nondiabetic patients, and the incidence would be even greater if one selected from the autopsy series only those diabetics who are known to have had diabetes for a minimum of five years. The first clinical method of studying the incidence of tuberculosis is the use of consecutive roentgenograms. This method showed at the Deaconess Hospital during 1930 and 1931 that, in 1,659 diabetic patients, active pulmonary tuberculosis was present in 2.5 per cent, or probably five times as frequently as in nondiabetics of similar age distribution. In 1938, among 366 patients similarly studied, the incidence was 3.0 per cent. A test of the incidence of tuberculous infection by means of the Mantoux skin test in children showed that up to 1932 about 45 per cent of the diabetic

TABLE 1

Incidence of tuberculin reactions among diabetic children, 1937

AGE	TOTAL CASES	NUMBER TUBERCULIN-POSITIVE
years		
1–5	8	5
6–10	27	9
11–15	32	11
16–20	2	1
	69	26

children had positive tests in Boston, and that was the same as in Vienna. In 1937 the positives had fallen a little, namely to 37 per cent. (Table 1.) The curves of mortality rates from diabetes and tuberculosis continue to converge. In Massachusetts the rate for pulmonary tuberculosis for 1936 was 40.4 per 100,000 persons and for diabetes 31.7 per 100,000. The city of Boston mortality rate for diabetes in 1937 was the highest ever recorded, 32.2 per 100,000 persons, and the rate for pulmonary tuberculosis fell to 45.3 per 100,000. In Boston twice as many deaths occurred in diabetic females as in males. The former almost universal tuberculous infection of the community is diminishing.

[2] Personal communication. Mr. Herbert Marks notes that, in the Registration area of 1925, cancer deaths totalled 95,735, in 273 of which tuberculosis was reported present. The corresponding figures for diabetes were 18,810 with tuberculosis also reported in 537. Age, sex and differences in duration should be considered.

The great increase in diabetes is due largely to better diagnoses, better treatment and the increased longevity of the population, bringing more people into the diabetes age period. It is striking that the mortality from tuberculosis among diabetics shows no fall comparable with the falling rate among the general population, even though allowance is made for the increase in longevity of diabetics.

AETIOLOGICAL FACTORS

A history of contact with active cases in the family or friends was obtained in 129 of these 364 cases. We have no accurate data as to the sputum tests in possible contacts and, therefore, these histories are subject to correction. Occupations of the group were variable. Indoor, sedentary occupations were recorded in 80 per cent. Exposure to hard metal or rocky dust was rare in this group. Three out of 50 deaths among diabetic doctors were due to pulmonary tuberculosis, 6 graduate nurses in this group had tuberculosis, of whom one had worked in a tuberculosis hospital. In his consideration of the factors in the decline of tuberculosis, Wolff (11) emphasized the constitutional factor and the nutritional factor. In the diabetic group this factor of nutrition stands out preëminently. The age and sex distribution in tuberculosis among diabetics is atypical, in that a large diabetic group is of necessity largely made up of individuals past forty years of age. Only 10 per cent of all cases of diabetes begin in childhood and 60 per cent of them begin after the age of forty years. Therefore, if pulmonary tuberculosis tends to develop in diabetic patients after prolonged duration of diabetes, naturally the population of the diabetic group will be predominantly in middle and late life. It is not strange, therefore, that among our deaths children have been few. Among 1,063 diabetic children treated between August, 1922 and 1937, 104 deaths occurred. In the first five years of this period the children who died did not live long enough to acquire tuberculosis and actually of the 35 deaths during that five-year period 91 per cent died from coma and the average duration of life of the child was only 2.7 years. During the next five years, among the 27 deaths, 2 were from tuberculosis. From 1932 to 1937 when the average duration of life was nine years and therefore the exposure to contact, the tuberculosis was greater; among the 42 deaths there were 7 from tuberculosis, or a percentage of 17. Thus, in the last fifteen years there have been 9 deaths from tuberculosis out of 104. Actually, the menace of tuberculosis increases with the duration of diabetes and, in fact, of the 10 deaths

among children whose duration of diabetes was ten and fifteen years there were 4, or 40 per cent, due to tuberculosis (3).

Among 258 fatal cases, no deaths occurred in the first decade and only 5 in the second decade. Only about a quarter of the deaths occurred under the age of forty years. The unusual predominance of the male rate after the age of thirty in proportion of 3 to 1 is yielding to the greater frequency of diabetes in females. Actually 50 per cent of the deaths recently have been in females. Diabetic women, however, are much less likely to continue industrial employment and, therefore, are less exposed to tuberculous infection. Although tuberculosis is emphasized as the great danger in youth, in diabetic patients it is also a great danger of late life. Actually, if one takes into account the total number of persons living at different age levels and the threat to his associates caused by an open lesion in an older individual, tuberculosis is a greater menace in old age than in youth. Race plays little rôle in this group of patients. About 10 per cent in this series were Jews, and Jews form about 13 per cent of the larger series of diabetic patients studied by Doctor Joslin.

PATHOLOGY

Distinctive morphological features of tuberculosis in diabetic patients have been sought to explain its great frequency. Curiously enough, there are comparatively few autopsies performed upon tuberculous diabetic patients in which the details of the examination are sufficiently complete to make careful comparisons with nondiabetic tuberculosis. At the Deaconess Hospital we have had only 15 autopsies performed upon tuberculous diabetics, and we were only able to gather 126 autopsies performed upon tuberculous diabetics from various sources. Wiener and Kavee (4) added 48 autopsies of diabetics, comparing them with 48 nondiabetic cases. The types of tuberculous lesions found at autopsy in diabetes, although varied, show a striking predominance of the pulmonary form. The larynx and intestines have been involved but rarely, actually only 3 in 126 diabetic cases tabulated. Tuberculosis of the intestines is more common in the ulcerative type of tuberculosis than in the chronic fibrous type. Nevertheless, only 2 cases of tuberculous ulcer of the intestines were found in 92 autopsies of diabetics reported by Seegen in contrast with 50 per cent to 80 per cent of cases dying of tuberculosis reported by Brown and Sampson (5). The menin-

ges and brain were not involved in a single case of the 126 autopsies, but isolated cases are occasionally reported.

Pleurisy with adhesions: A striking feature was brought out by Wiener and Kavee. They found that tough fibrous plural adhesions were twice as common in nondiabetic patients as in the diabetic. This fact, while suggesting at first lack of the defensive response with fibrosis, also suggests an explanation of the clinical fact that in diabetic patients it is so often easy to use pneumothorax with excellent results. Pleurisy does occur in all its forms in diabetics, but in our series of 364 cases onset of tuberculosis with pleurisy and effusion was notably rare.

Healed tuberculosis may be found either as small healed foci in the lungs, or what is more important, numerous healed and healing processes in the lungs of patients who, nevertheless, have active pulmonary tuberculosis which causes death. Unquestionably, in our series of autopsies pleural adhesions and small calcified foci were entirely disregarded. A complete picture therefore of the extraordinary power of healing possessed by many diabetic patients, if they are given a good chance, is not available.

Caseation: Tuberculosis in diabetics has often been described as characterized by large extending areas of caseation. Caseation, as a term applied to coagulation necrosis, occurs in the nondiabetic tuberculous as well. Just as cheese is a mixture of coagulated protein and finely distributed fat, so in caseation there is coagulation of tissue protein associated with deposition of fat. Again we are reminded of the disorders of the fat metabolism in the diabetic.

It is true that acute generalized tuberculosis, such as occurs in childhood, is rare in diabetes. Tuberculosis of the joint surfaces is uncommon. If one compares the pathology of tuberculosis in the diabetic with that of the Negro, certain features are similar, such as the frequency of acute pneumonic lesions and extensive caseation. The diabetic seems to have had normal resistance as judged by the number of calcified foci remaining from earlier infections, but in some manner loses his resistance after the onset of the diabetes.

If we turn now to the distinctly biological aspect of the problem, we will consider first the tubercle bacillus itself. Certainly in our own cases the ordinary acid-fast staining organism was found in the sputum in about the same proportion as in nondiabetics, so that we could not support the old statement often heard that the tubercle bacillus was difficult to find in the sputum of the diabetic. The variations in form

and growth of the organism, which have been studied in recent years particularly by Petroff in this country and by other bacteriologists elsewhere, suggest that possibly in the diabetic patients differences in form of the organisms under slightly different cultural conditions might occur.

A hypo-allergic state, especially following pneumococcal infection, has been stressed by Thiéry (1) and Labbé as explaining the explosive tuberculosis of diabetics.

Lipoid changes in diabetic tissues: One wonders whether the metabolic characteristics of the diabetic patients might have a bearing upon the growth and development of the organism in the diabetic lung. No other organism has been so carefully studied as the tubercle bacillus. The distinctive feature is the waxy substance, although protein and carbohydrate and fatty substances with mineral residue are present. The lipids compose 10 to 40 per cent of the dry weight. We can best refer the reader to the summary by Long of the more important chemical and metabolic features of the organism in relation to nutritional requirements of the tubercle bacillus, and to the recent study by Boissevain and Schultz (10) of a special fat-soluble growth promoting substance. Its mineral requirements are simple. It obtains its nitrogen from the amino group; its own proteolytic enzymes are weak, so that it does not grow well on whole protein. However, ammonium salts and amino-acid amides are sufficient. The protein metabolism is seriously disturbed in diabetics during serious acidosis, particularly during coma. Great loss of weight and destruction of protein occur. Occasionally in severely uncontrolled diabetic patients nitrogen excretion of 25 to 30 g. occurs in twenty-four hours. During acidosis values from 30 to 35 g. have been reported. Recurrent or mild persistent acidosis is naturally more common. Glycerol appears to be the only alcohol acting as a source of carbon for the organism. In the diabetic the disturbance of the fat metabolism must at times set free an unusually abundant amount of glycerol in the blood and tissue fluids. Unfortunately, no analyses of the blood for glycerol were made during diabetic coma. It has seemed to many students that in some way the cultural conditions favorable to the growth of the tubercles are linked with the fat metabolism.

Lipid content of diabetic lungs: One of the most characteristic features in the tissues of diabetic patients is the remarkable alteration of the fat content of certain organs. The removal of fat from one tissue and its

deposit in another has been correlated with certain well recognized changes in the severity and intensity of the diabetes. Thus certain cases of diabetic coma, occurring particularly in emaciated patients of long duration, demonstrate a marked infiltration and increase in the fatty content of the liver. Under similar circumstances, especially if the patient is cachectic, an increase of blood lipids consisting of cholesterol, fatty acids and often free fat occurs, such that there may be a deposit in the spleen producing the characteristic fat-filled foam cells. Recent analyses of lipid content of livers removed at autopsy at the Deaconess Hospital by Miss Halliday and Miss H. Hunt have shown in 7 nondiabetics an average cholesterol content of 177 mg. in comparison with 417 mg. in 7 diabetics. The average phospholipid content for the same nondiabetic livers was 1,774 mg. whereas for the diabetic group the average value was 1,949 mg. per cent. Excessive lipid content of the liver and blood can be controlled by means of insulin so that a patient may lose the excessive fat within a few hours or days with proper treatment, the excessive fat being either metabolized or deposited in more normal tissue depots. A chronic type of fatty change is the excessive atherosclerosis found in diabetics characterized by a rich deposit of cholesterol and other fatty substances in the intima of the muscular arteries.

It has long been known that in degenerative conditions of the brain and central nervous system a decrease in the lipid content of the tissues may be found. Actually in diabetics, Jordan, Randall and Bloor (6) found that the lipid content of nerves, studied in amputated legs or at autopsy, was materially reduced in comparison to the normal. Although this change was often correlated with vascular disease, it did seem more definitely related to diabetic neuritis. It is clear, therefore, that alterations in lipid content in the tissues of diabetics can be correlated with clinical conditions. It becomes of considerable interest, therefore, to know whether or not the lipid content of lung tissue could be related in any way to the resistance of the diabetic lung to tuberculous infection. Analyses of lungs removed at autopsy at the Deaconess Hospital were carried out in Professor Bloor's laboratory. The method was to remove a section of lung tissue from the upper anterior portion of the lung where oedema and postmortem changes would be least important. The specimen was immediately placed in especially prepared solutions for chemical analysis. It must be admitted, however, that in the older group, including especially patients with coronary disease,

TABLE 2

Lipid content of lung tissue in 26 diabetics and 2 nondiabetics

PATHOLOGY NUMBER	DIABETIC CASE NUMBER	SEX	AGE AT DEATH	DURATION OF DIABETES	CAUSE OF DEATH	PATHOLOGY			LUNG LIPIDS, GRAMS PER 100 G. WET TISSUE		
						Pancreas	Lungs	Miscellaneous	Phospholipid	Cholesterol	Ratio Phospholipid / Cholesterol
			years	*years*		*grams*					
25,531	*	F	57	12	Coronary thrombosis	100		General arteriosclerosis, moderate infarct; fatty liver	2.44	0.42	5.8
31,660	13356	M	61	17	Primary carcinoma, bronchus, metastases to liver, pancreas, spleen, etc.	90	Carcinoma	Coronary arteriosclerosis	1.82	0.56	3.3
25,543	2021	F	52	14	Coronary thrombosis	50	Atelectasis both lower lobes	Aorta: cholesterol clefts, numerous lipoid-laden phagocytes, slight arteriosclerosis, cardiac infarction	1.71	0.34	5.0
24,559	12130	F	62	2	Cardiac infarction	90	Pulmonary embolism, healed pulmonary tuberculosis	Aorta: focus of many large cholesterol clefts, fatty infiltration of liver	1.63	0.54	3.0
29,077	2903	M	75	15	Abscess of lung	90	Bronchiectasis	Aorta: cholesterol clefts and foci of lipoid filled phagocytes; lipoid histiocytes of spleen	1.60	0.42	3.8
24,142	13150	F	50	4	Acute purulent pericarditis	No weight	Healed apical tuberculosis, pulmonary congestion	Slight fatty infiltration of liver	1.55	0.41	3.8
31,185	14756	F	23	2	Diabetic coma	60	Oedema, chronic fibroid tuberculosis, apex of left lung	General arteriosclerosis	1.50	0.38	3.9
24,502	15296	F	75	24	Cerebral thrombosis, acute pericarditis	130	Congestion	Aorta: some cholesterol deposition; one cholesterol stone in the gall bladder	1.27	0.36	3.5

23,783	5793	M	64	14	Coronary thrombosis	140	Healed pulmonary tuberculosis	Aorta: some cholesterol deposition in subintima layer with hyalinization in surrounding regions; fatty infiltration of liver	1.25	0.43	2.9
23,365	3194	F	62	12	Acute endocarditis	15 Atrophy	Healed pulmonary tuberculosis	Aorta: some cholesterol clefts; rheumatic endocarditis (old), recent endocarditis and pericarditis, moderate arteriosclerosis	1.24	0.34	3.6
32,879	*	M	61	5	Cerebral haemorrhage	100	Passive congestion; bilateral hydrothorax	General arteriosclerosis	1.23	0.49	2.5
29,627	4247	M	69	14	Carcinoma of sigmoid	20	Slight, early bronchopneumonia	Aorta: cholesterol deposition, fatty metamorphosis of liver, arteriosclerosis	1.12	0.43	2.9
28,150	11362	M	61	3	Cardiac decompensation	80	Atelectasis left lower lobe	Nephrosclerosis, generalized arteriosclerosis, coronary sclerosis	1.08	0.29	3.7
23,669	7465	F	56	10	Coronary heart disease	25 Atrophy	Hydrothorax, left	Marked arteriosclerosis, coronary sclerosis	1.02	0.28	3.9
32,880	14660	F	60	2	Carcinoma, vagina	105	Left, lower lobe congested	Fatty degeneration of liver	0.95	0.40	2.4
24,355	13213	F	82	19	Gangrene	120	Pulmonary oedema	Aorta: few small cholesterol clefts, one cholesterol stone in gallbladder of mulberry type	0.93	0.23	4.0
31,750	2681	M	58	14	Cerebral thrombosis	80	Calcified primary tuberculosis	Severe cerebral arteriosclerosis	0.89	0.35	2.5
31,241	14056	F	71	1	Coronary sclerosis	120	Pulmonary congestion and oedema; bilateral hydrothorax	Myocardial infarction (old and recent), fatty metamorphosis of liver with central necrosis	0.89	0.35	2.5
28,899	14301	M	65	1	Coronary occlusion	90	Pulmonary emphysema, congestion, hydrothorax	Aorta: large placques, cholesterol crystals; congestion of liver and spleen	0.89	0.34	2.6
29,792	9479	F	46	13	Sepsis right thigh	80	Bilateral hydrothorax, healed tuberculosis, lymphadenitis	Fatty liver, central necrosis	0.88	0.42	2.1

Note: Lipid values are expressed in milligrams per 100 grams of moist tissue.

* Patients of Dr. F. Gorham Brigham, to whom we express appreciation.

TABLE 2—*Concluded*

PATHOLOGY NUMBER	DIABETIC CASE NUMBER	SEX	AGE AT DEATH	DURATION OF DIABETES	CAUSE OF DEATH	PATHOLOGY			LUNG LIPIDS, GRAMS PER 100 G. WET TISSUE		
						Pancreas	Lungs	Miscellaneous	Phospholipid	Cholesterol	Ratio Phospholipid / Cholesterol
			years	*years*		*grams*					
31,132	14683	F	34	10	Peritonitis	150		Early central necrosis of liver	0.85	0.27	3.1
23,524	12882	F	27	6	Hypoglycaemia	Normal size			0.82	0.24	3.4
23,304	8036	M	76	7	Rupture of arteriosclerotic aneurysm of aorta	50			0.73	0.22	3.3
30,116	*	M	49	5	Chronic tubular nephritis	80	Hydrothorax	Fatty liver; tubular nephritis	0.69	0.24	2.9
28,553	8362	F	59	7	Pulmonary embolism, paroxysmal tachycardia	100	Pulmonary oedema	Aorta: cholesterol clefts; central necrosis of liver	0.67	0.43	1.6
32,578	15099	F	66	6	Coronary thrombosis	70		Fatty liver, severe coronary sclerosis	0.63	0.33	1.9
Non-diabetics											
31,309		M	75		Pulmonary embolism	100	Pulmonary infarcts	Carcinoma of prostate; marked arteriosclerosis	0.94	0.29	3.2
23,686		M	71		Renal insufficiency Prostatic hypertrophy	110	Pneumonia	Cholelithiasis	0.89	0.31	2.9

terminal congestion of the lungs, especially due to heart failure, may have appreciably lowered the figures for lipoid content, although definite efforts were made to avoid taking tissue in dependent portions of the lungs, and to avoid inflamed areas if such were present.

Very few figures are available for lung tissue in any animal. In rats, the lungs contained about 2 per cent phospholipid and 0.45 per cent cholesterol; in beef lung, the phospholipid is 1.5 per cent and the cholesterol 0.22 per cent. In human lung (two years) the phospholipid is 1.69 per cent and the cholesterol 0.46 per cent. All these figures are upon the basis of moist weight. Fallon (12) found that the amount of phospholipid in the lungs of rabbits increased rapidly after intratracheal injection of quartz particles.

In table 2 are listed clinical data regarding 26 diabetic and 2 nondiabetic patients together with the values for phospholipid and cholesterol content of the lungs. Values are given in grams per hundred grams weight of wet tissue. The first 12 cases listed are those in whom the phospholipid value exceeded 1.10, arranged in descending order; 7 of the 12 were females. Only 1 (31,185) was under thirty years of age, 3 were between fifty and sixty years, 6 between sixty and seventy years, 2 were seventy-four years old. Two nondiabetic patients at the foot of table 2, aged seventy-one and seventy-five years, showed values for phospholipid of 0.94 and 0.89. It is striking that among these 12 cases only 3 were cases of short duration. The remainder had had diabetes from twelve to sixteen years. The 3 who had had diabetes a short time included a young woman (14756) who died in coma and who had healed tuberculosis at one apex; another woman (13150) who died of acute pericarditis with associated healed tuberculosis and fatty liver; and a woman (12130) who died of cardiac infarction and, in addition, healed or healing tuberculosis. Actually 5 out of the 12 patients showed evidence of healed or healing tuberculosis at an apex. One diabetic, case 25,531, a patient of Dr. F. G. Brigham, had a value of 2.44 mg. She died of coronary thrombosis and had a fatty liver. Fat-filled livers were noted in 4 cases and in 5 there was lipoidosis of the spleen. The remaining 14 diabetics of this series who did not have an increase in phospholipid content included a physician who had a calcified primary tuberculous focus in one lung, and a woman, forty-nine years of age, with diabetes of twelve years' duration, who showed a small focus of healed tuberculosis.

If we turn to the cholesterol figures, the 2 normal cases had cholesterol

concentrations of 0.29 and 0.31 per cent, whereas the diabetic cases ranged from 0.23 to the maximum of 0.54 per cent. Fifteen of the 26 diabetic patients had cholesterol values of 0.35 per cent or higher and in this group we find 6 of the patients with healed apical tuberculosis and again the almost constant marked arteriosclerosis and fatty liver.

Actually in this small group, the cases with higher lipid concentrations in lung tissue showed much more evidence of past tuberculous infection. Further study is clearly needed, since the majority of the cases showed lower lipid concentrations than normal.

The low phospholipid value is to be considered together with the low phosphorus content of diabetic cataracts, described by Carey and Hunt, Waite and Beetham (13). The frequency of the development of tuberculosis in diabetic patients who have true diabetic cataracts has been stressed by Himsworth (14). It may well be that the low phosphorus values are related to the carbohydrate metabolism in such a manner as to affect the resistance to tuberculosis.

CLINICAL

Cases of glycosuria, not proved to be true diabetes, have been excluded from this series of 364 patients. For a diagnosis of pulmonory tuberculosis, the persistent finding of fine râles at the apex, X-ray evidence or sputum containing tubercle bacilli were accepted. The outstanding clinical fact is the rarity of cases with minimal lesions. Actually, prior to the discovery of insulin, we have been unable to find any proved case of diabetes and tuberculosis in which the tuberculosis had been discovered in a minimal stage. In this series of 364 cases we have only 17 and one of these was discovered solely because that child had her lungs X-rayed every four months for four years until the first lesion about the size of a five-cent piece appeared. Now, five years later, after violating all rules, she has a bilateral process and has received bilateral pneumothorax.

Of the 7 cases discovered since 1932 and listed in table 3, in 3 (6532, 5692 and 5635) the diabetes began during childhood and X-ray examinations were made as a routine follow-up because 2 had had coma and the third had had an X-ray film with suggestive increase in markings some three years previously. Case 4935 developed spontaneous pneumothorax with the slightest of symptoms. The other three patients had X-ray examinations made during the course of a hospital stay, occasioned by infection of a toe in cases 15959 and 13200. The charac-

teristic features of these early lesions in the entire group of 17 minimal cases were (*1*) localization in the apex in 7 cases; (*2*) softness and lack of a sharp marginal definition of the shadow; (*3*) the fact that the process was below the clavicle and at the level of the hilum of the remaining ten.

TABLE 3

Seven diabetic cases with minimal pulmonary lesions

CASE NUMBER	SEX	AGE IN 1938	DURATION OF DIABETES	SIGNS AND SYMPTOMS AT TIME OF X-RAY FILM	LOCATION OF LESION	LATER COURSE
3133	F	42	16	Cough; dyspnoea	2.5 cm. area of density in left lung field, fourth anterior interspace	Living in January, 1937
4935	M	55	13	Spontaneous pneumothorax about 10/5/37; slight dull ache on left side of his chest	In sixth and seventh interspaces on right in region of former pneumothorax there is an area of increased density	Living in November, 1937
5635	F	25	11	Diarrhoea	1.5 cm. area in the fifth interspace on the right	Living in July, 1937
5692	M	20	11	No signs	Third and fourth interspaces show area of increased density suggesting parenchymal involvement. December, 1934	Living in May, 1937
6532	M	28	11	No signs	Area of opacity, fifth interspace posteriorly, outer half of chest. May, 1937	Sanatorium, living in July, 1937
15959	F	70	9		Small area running outward from right hila to periphery on level with seventh interspace posteriorly	Living in October, 1937
13200	F	67	7		Small area of density right lung level with seventh interspace posteriorly. July, 1937	Living in April, 1937

All 7 of these recent cases are living in contrast with the first 10, of whom 5 are dead.

Case-finding by X-ray follow-up: If pulmonary tuberculosis is ever to be found in a reasonably early stage in diabetic patients, all coma cases must have reëxaminations at stated intervals after recovery from coma and all cases with suspicious parenchymal changes or calcified tracheobronchial lymph nodes should have a similar follow-up. During 1937,

108 such chest X-ray films were taken. Of 87 who had previously had diabetic coma, 4 were classified as showing suspiciously increased markings in the parenchyma, 9 had tracheobronchial adenitis with calcification, 1 showed old healed tuberculosis, and 1 showed an incipient lesion. Among 21 cases in whom X-ray films were taken because of previous somewhat suspicious reports, 5 were still regarded as suspicious, 1 showed old healed tuberculosis, 1 showed an active but minimal lesion which has since cleared appreciably after nine months in a sanatorium.

In contrast to these minimal cases and the cases picked up by routine X-ray examination, 77 of the remainder of the series were discovered after hospital admission, as a group. They again demonstrate the startingly advanced character of most pulmonary tuberculosis when discovered in diabetics only after symptoms have developed. Thus of these 77 cases, 27 are already dead; 15 of these died within six months of the discovery of tuberculosis. The only chance of discovering tuberculosis in a diabetic person in a reasonably early stage is to insist upon repeated X-ray examinations of the chest.

TABLE 4

364 cases of combined tuberculosis and diabetes

	AGES AT ONSET OF DIABETES								
	0–9	10–19	20–29	30–39	40–49	50–59	60–69	70–79	80+
Diabetes	6	32	46	70	77	85	39	9	
Tuberculosis	2	24	50	66	51	85	60	19	1

Clinical course: In table 4 are shown, for 364 cases, ages at onset by decades of both tuberculosis and diabetes. Actually, 83 per cent of this series developed tuberculosis following the onset of their diabetes. Nevertheless, it must be remembered that in the vast majority of these patients the primary infection was earlier in life. It is the reactivation and the development of adult type progressive pulmonary tuberculosis that concerns us. It is true in occasional cases that such adult type tuberculosis has been present before diabetes and had become quiescent until the diabetes began. It is also true that many prospective diabetics who develop tuberculosis early in life will die of it before reaching the age where the diabetes would have had its onset.

The clinical course of the tuberculosis was variable. The onset of tuberculosis in diabetes is no more insidious than in nondiabetics.

Symptoms and physical signs are no more rare in the diabetic with tuberculosis than in the nondiabetic, although errors are often made in ascribing symptoms to the diabetes rather than suspecting tuberculosis. The signs are usually there if we but look for them carefully enough and frequently enough. Case 8712 had a negative chest X-ray film in April, 1933. He returned to the hospital in October, 1933 with advanced pulmonary tuberculosis with cavitation and was dead within two months. A case with such rapid development and extension is the exception rather than the rule. In the majority of our cases the onset was insidious and perhaps could be best described as grippe-like. Occasional cases of pleurisy with effusion occurred and 18 per cent of the cases reported haemoptysis at some time, although this was rarely the initial symptom.

In the course of the diabetes a striking feature in the adult was rapid loss of weight during the months or years preceding the development of tuberculosis. In 219 cases the average loss of weight was 42 pounds and loss of weight in excess of 75 pounds occurred in 19 cases. Sixty cases, or almost 20 per cent, were known to have had diabetic coma. If we had reliable data for the entire series, it is likely that the incidence of severe acidosis, even though it did not reach the stage of full coma, was probably close to 50 per cent of the series. The degree and severity of the diabetes as judged by the glycosuria and carbohydrate tolerance do not permit one to say that one type of diabetes is more apt to develop tuberculosis than another. It is true that, as tuberculosis advances and emaciation comes on, oftentimes the diabetes nearly disappears, but such increases in tolerance are occasionally seen in association with other types of infection even of a septic character if they are chronic and of long duration. The important question in the course of the diabetes is largely the degree of control and the maintenance of proper nutrition. In one instance, case 7131, a nervous and overconscientious girl restricted her diet too greatly in order to keep sugar-free and undoubtedly hastened the development of tuberculosis by marked undernutrition.

Tuberculosis in juvenile and adolescent diabetics: To the 17 cases of pulmonary tuberculosis developing in patients in whom diabetes began before the age of 20.1 years, reported in 1934, we can add 15 new cases developing since that time. In this group of 32 cases there are 18 whose diabetes began before their fifteenth birthday. The incidence, therefore, of pulmonary tuberculosis of the adult type developing in 1,126

children whose diabetes developed before the age of fifteen years is 1.6 per cent. If this is compared with the incidence in 140,000 school children studied by Pope (7), in whom the development of tuberculosis was 0.12 per cent, the frequency in our diabetic children is about 14 times as great.

In table 5 are listed 15 recent cases of whom 3 have already died. Six are males and 9 are females. After having diabetes an average of 7.1 years, it is to be noted that the duration of life after the discovery

TABLE 5

Fifteen cases of pulmonary tuberculosis in juvenile and adolescent diabetics, 1932–1937

CASE NUMBER	SEX	ONSET OF DIABETES		ONSET OF TUBERCULOSIS	INSULIN*	LIVING OR DEAD	DATE	FOLLOW-UP		CAUSE OF DEATH
		Date	Age					Height	Weight	
					units			*inches*	*pounds*	
3332	M	1–23	17.4	2–37	32	L	3–37	65	139	
4261	F	11–23	9.0	6–33	6 + *30*	L	4–38	64	119	
5181	F	7–25	20.0	1934	24 + *16*	L	4–38	63	120	
5635	F	1–26	12.7	11–36	40	L	1938	64	129	
5692	M	11–26	9.1	12–34	42	L	5–38	61	95	
6532	M	9–26	17.2	5–37	*37*	L	7–38	66½	115	
7047	F	6–28	11.0	5–32	102	D	1–35	65	117	Tuberculosis
7131	F	5–28	15.4	2–35	30	L	3–38	63	133	
7538	F	9–26	16.0	1934	21	D	10–9–34	62	98	Pulmonary tuberculosis
8754	M	11–29	20.0	3–36	27	L	1938	69	110	
10020	F	3–31	15.5	5–37	30 + *64*	L	5–38	66	120	
11600	M	11–20	18.5	1–33		L	5–38			
12171	M	12–32	13.2	2–36		L	1938			
12385	F	1–29	10.0	11–33	36	D	1–9–34	56	67	Pulmonary tuberculosis
12757	F	1–25	1.1	4–36	46	L	8–38	53	82	

* Italic figures indicate protamine-insulin.

of tuberculosis in these 3 cases was only a matter of months. On the other hand, the duration of diabetes in the 12 cases still alive was 8.8 years on the average before tuberculosis was discovered. All cases received insulin, except 2, whose records in sanatoria we have not yet obtained.

Among 201 diabetic children studied at the Deaconess Hospital, 42 per cent of the first decade and 74 per cent in the second had calcified tracheobronchial lymph nodes. Tuberculosis developed most frequently among the least well controlled diabetics. A free diet even

with insulin encourages tuberculosis. Undoubtedly contact with an open case has been present, but the development of progressive tuberculosis in young diabetics is measurably influenced by the type of diabetic treatment carried out.

Diet and tuberculosis: The object of treatment in tuberculous diabetics should not be dictated by a slavish regard for sugar-free urine and a normal blood sugar, if that attitude leads to the use of a diet too poor in carbohydrate or to undernutrition or to the use of too large doses of insulin which may provoke an overactivity of the counter-regulatory and opposing influences in the organs.

1: Glycogen impoverishment leads to acidosis, which may be of acute life-threatening type as in coma or in lesser degree to weakness and loss of vitality and resistance in the organs. It also leads to hypoglycaemia and serious insulin reactions.
2: Hypercholesterinaemia is to be avoided since it is favorable to the development of arteriosclerosis manifested in angina pectoris, apoplexy and gangrene.
3: On the other hand, in toxic tuberculous patients, a low value for cholesterol in the blood plasma may be accompanied by grave insulin reactions and may itself indicate an increased susceptibility to the hypoglycaemic effect of insulin.

Bertram (8) believes that haemorrhages are in no sense due to insulin but rather to a diet improperly balanced with regard to carbohydrate. He feels that the haemorrhages are far more likely due to overactivity of the opposing regulatory mechanisms, which leads to an outpouring of adrenalin, increased tonus in the peripheral vessels and an increase in the minute volume in the lungs and so to increase of blood pressure. Such haemorrhages occur in many other types of conditions as well as tuberculosis, indicating that the important thing is not tuberculosis but the susceptibility of the diabetic to vascular damage when the adrenalin response is too great. In general, then, the diet of a diabetic tuberculous patient should have from 150 to 200 g. carbohydrate and from 70 to 130 g. fat. Sample diet for use with tuberculous patients may be classified as follows, on the basis of a patient weighing 132 pounds:

	CARBOHYDRATE	PROTEIN	FAT	CALORIES
	grams	*grams*	*grams*	
1. Standard diet	150	80	100	2,100
2. Surgical diet, before operation	200	75	70	1,730
day of operation	100	20–30	40–50	880
3. Diet to increase weight	250	87	120	2,436

In table 6 is summarized the treatment of 20 patients with diet and insulin, particularly protamine-zinc-insulin. It is noted that in two instances the number of calories prescribed per kilogram body weight is less than 30. In each, the patient at the time was confined to bed for a considerable period of time because of the surgical treatment of an

TABLE 6

20 tuberculous diabetics treated with protamine-zinc-insulin

CASE NUMBER	SEX	AGE IN DECEMBER, 1937	DURATION		HOSPITAL DISCHARGE DIETS					WEIGHT	CALORIES PER KILOGRAM	INSULIN DOSES	
			Diabetes	Tuberculosis	Date	Carbohydrate	Protein	Fat	Calories			RI*	PZI*
												units	*units*
4261	F	23.0	14.0	4.4	9–20–36	159	71	90	1,730	117	32.7	6	30
4856	F	49.8	14.8	7.9	2–38	150	80	110	1,910				80 at 7:30 a.m. 30 zinc-insulin crystals
4935	M	55.1	13.1	0.6	10–37	152	79	101	1,825	116	34.6		28
5181	F	32.4	12.4	3.9	2–37	300	87	91	2,367	120	43.3	24	16 one hour before supper
6287	F	27.5	15.5	5.4	1–38	180	96	95	1,969	92	47	12	28
6532	M	28.5	11.2	0.6	5–37	161	86	104	1,924	114	37	10	30
10020	F	22.7	7.0	0.5	11–37	149	82	100	1,824	120	33.4	30	64
10491	F	73.2	6.2	3.9	7–37	142	71	103	1,779	88	44.4	4	40
11327	F	36.3	5.3	1.2	9–37	150	80	110	1,910	132	32	26	24
12496	M	72.1	5.1	5.1	1–37	135	65	90	1,770	105	31.4		8
13200	F	66.9	7.9	3.2	2–37	149	60	81	1,565	137	25.1		8
13709	F	52.4	8.4	27.4	5–37	140	73	92	1,680	98	36		24
13874	F	20.5	2.7	2.2	9–37	168	74	87	1,751	101	38.1	4	28
14288	F	59.4	14.7	0.1	11–37	141	57	84	1,548	123	27.6	12	30
14953	F	39.8	3.8	1.1	11–36	180	80	110	2,090	111	41.6		28
15083	F	65.4	2.9	1.3	12–36	171	77	100	1,892	123	32		30
15131	F	49.4	11.2	1.0	12–36	170	82	101	1,917	120	35.1		52
15442	M	69.6	0.6	24.7	6–37	147	76	92	1,720	147	25.7		10
15959	F	69.3	9.4	0.4	8–37	153	73	100	1,804	105	37		12
15976	F	48.6	0.5	0.3	9–37	153	73	92	1,720	98	38.6		10

* RI = unmodified insulin; PZI = protamine-zinc-insulin.

infected foot. Each of these 2 patients was free from fever and the tuberculosis more or less quiescent. Indeed, the diet for the entire group represents diets prescribed at the Deaconess Hospital where the patients were under control preparatory to their transfer to sanatoria. These diets should, therefore, be regarded from the point of view chiefly as adjustment to the diabetes rather than as diets intended for long

continued use in the management of the tuberculosis. The striking fact appears that the diabetic patient with tuberculosis does not require any great increase in the amount of insulin in relation to his diet and body weight as compared to the diabetic without tuberculosis.

Protamine-zinc-insulin: The advantages of protamine-insulin in treating pulmonary tuberculosis are easily seen. In sanatorium practice it reduces the frequency of injections from two or three times a day to a single treatment before breakfast. Furthermore, the steady and long continued action of protamine-zinc-insulin makes it possible to have a steady and constant formation of glycogen and it reduces the danger of severe insulin reactions. The peculiar property of protamine-insulin which makes possible marked gain in weight is of fundamental importance. This property has been studied both in animals and in human beings and especially described by Sherrill (9). Nevertheless, it is still easy for tuberculous patients, and particularly the emaciated advanced patient, to develop spontaneous hypoglycaemia and therefore still easier to develop hypoglycaemia under insulin treatment. Case 11419, male, 48 years of age, came into the Deaconess Hospital having been taking from 5 to 10 units of insulin. He was sugar-free, had oedema, and, when we found that the fasting blood sugar was as low as 60 mg. in the morning, insulin was omitted and his diet increased to 250 g. of carbohydrate a day. In addition to that he was given carbohydrate at his bed-side and urged to eat frequently between meals. One morning at seven o'clock he was apparently dying but revived promptly with an intravenous injection of glucose solution. He developed spontaneous hypoglycaemia with a blood sugar of 0.2 per cent (20 mg.) without any insulin whatever. Case 15976, age 48, onset of diabetes in May, 1937, was discovered to have advanced tuberculosis in September, 1937. At this time her weight had fallen from 160 to 90 pounds. In the hospital the urine cleared up rapidly. She left the hospital taking 10 units of protamine-insulin a day. At the sanatorium the insulin dose was increased for a time and then came a period when the urine was sugar-free for a week with only 20 units of insulin once a day. One morning at 6:30 she was noted to behave queerly; by eight o'clock her neck was stiff and she had double Babinski signs. A physician in attendance considered tuberculous meningitis, probably because the pulmonary tuberculosis was advancing generally. However, insulin was omitted and to everyone's surprise within a few hours her symptoms cleared up. She died within a month of pulmonary tuberculosis.

Diabetic coma: In table 7 is summarized the treatment of diabetic coma in a school girl who had active and advanced pulmonary tuberculosis but who showed neither fever nor râles during coma. In the treatment of diabetic coma it is fundamental to give sufficient insulin to bring about such an improvement in the carbohydrate metabolism that the blood sugar falls and the carbon dioxide combining power of the blood rises. Second, to treat the intense dehydration and loss of base from body tissues by administration intravenously and subcutaneously of sufficient salt solution to restore body fluid and electrolytes. On

TABLE 7

Treatment of diabetic coma and pulmonary tuberculosis—case 7047, schoolgirl, age 16, May 10, 1934—died of tuberculosis in January, 1935

	URINE		BLOOD		BLOOD PRESSURE	INSULIN	SALT SOLUTION	BLOOD TRANSFUSION	CAFFEINE	ADRENALIN 1:1000	EPHEDRINE	GINGER ALE AND ORANGE JUICE	GLUCOSE
	Sugar	Diacetic acid	Sugar	Carbon dioxide combining power									
	per cent		*mg.*	*vol. per cent*		*units*		*cc.*	*g.*	*cc.*	*mg.*	*cc.*	*g.*
Admission	4.8	++++	1,050	4	70/?	100	1,000 cc. iv		0.45	1	50		
							1,500 cc. sc						
2 hours			700	7	88/?	200			1.00				
4 hours					70/?	200	500 cc. iv						
							1,500 cc. sc	400	2.00	1			
8 hours			410	6	96/22	100							
12 hours	Trace		130	10	100/60		600 cc. iv					500	
16 hours	0	0	160	16								300	20
Totals in 16 hours						600	5,100 cc.	400	3.45	2	50	800	20

admission, this girl was unconscious and the blood pressure was barely obtainable at 70; her eye balls were soft; she had vomited repeatedly and gastric lavage yielded tarry black stomach content. An immediate injection of 100 units of insulin was given even before we learned that the blood sugar was 1,050 mg. per 100 cc. In the next eight hours she received a total of 600 units of insulin and by that time the blood sugar had fallen to 410 mg. She also received a total of 4,500 cc. of salt solution as well as one blood transfusion because her blood pressure failed to rise. As we look back now, it is unlikely that the drugs (caffeine, ephedrine and adrenalin) given her had any considerable effect. The

value of the blood transfusion is also doubtful in view of later experience and would not now be employed.

Prognosis: The utterly hopeless prognosis given to the diabetic patient with tuberculosis before the use of insulin was based upon the fact that tuberculosis was always discovered in an advanced state. Tuberculosis discovered in an early stage was unknown. The remarkable efficiency of insulin and modern dietary treatment in preventing death from coma and maintaining good nutrition, as well as the use of surgical procedures, such as collapse therapy, have brought almost as spectacular improvement in the outlook for the tuberculous diabetic as has the use of insulin in childhood diabetes.

The hope, however, for the future lies chiefly in earlier diagnosis and this means more frequent use of X-ray for young diabetic patients who

TABLE 8

Duration of diabetes and pulmonary tuberculosis in 258 fatal cases

PERIOD	NUMBER OF CASES	DIABETES	TUBERCULOSIS	TOTAL DIABETIC DEATHS	PER CENT TUBERCULOSIS
		years	*years*		
1898–1914, August 7	19	5.4	2.7	342	5.6
1914, August 8–1922, August 7	47	5.2	3.0	805	5.8
1922, August 8–1930	87	6.2	3.1	1,278	6.8
1930–1938, July 29*	105	10.1	4.0	1,880	5.6

* We are indebted for the tabulation of these data to the courtesy of Mr. Herbert Marks of the Statistical Bureau of the Metropolitan Life Insurance Company.

have positive tuberculin tests and examinations for older patients, especially those who have had diabetic coma, at stated intervals as a routine check-up. The favorable course of tuberculosis in youthful diabetics when discovered early is well illustrated in case 2179, a boy whose diabetes began in 1921 at the age of sixteen years and whose tuberculosis was moderately advanced in 1929. He was alive in 1937 and in good condition. Case 5413, a boy whose diabetes began in 1926 at the age of fifteen, developed tuberculosis with positive sputum in 1932. He is at work now after having spent more than a year in a state tuberculosis hospital.

Effects of insulin can be illustrated by the fact that fatal cases treated with insulin lived 8.9 years and those treated without insulin lived 5.9 years after the onset of diabetes. In 1937 we have 20 cases alive more than five years after the discovery of active pulmonary tuberculosis, the average being twelve years. Actually, the prognosis for tubercu-

losis in a diabetic patient may be better than in a nondiabetic. When tuberculosis has developed in a diabetic patient untreated with insulin, a dramatic improvement in nutrition as well as in the tuberculosis with proper insulin and dietary treatment results.

More significant data are obtained from a consideration of table 8 giving the duration of diabetes and pulmonary tuberculosis in 258 fatal cases. It is seen that in each period of treatment beginning in 1898 up to July 29, 1938 there has been a steady prolongation of life after the onset of diabetes so that the average duration of life has risen from 5.4 years to 10.1 years. The improvement in the duration of life after onset of tuberculosis is less striking in actual years but almost as great in terms of percentage. The increase from 2.7 years to 4.0 years represents an increase of 50 per cent. In the last two columns are given the figures which bear upon the chance of the average diabetic patient developing tuberculosis. It can be seen that there has been no great change although the decrease from 6.8 per cent to 5.6 per cent is a hopeful sign.

The prognosis for activity outside of the sanatorium is vastly improved. Diabetic patients make excellent subjects for pneumothorax and even for thoracoplasty, both of which methods of treatment have been in common use in our diabetic patients in the sanatoria to which they have gone. Again the success of these surgical forms of treatment should be greatly enhanced in the future by earlier diagnosis of the tuberculosis.

SUMMARY

1. Study of the various aetiological factors in 364 diabetic patients with pulmonary tuberculosis points to the disturbed nutrition of diabetes as next in importance to contact with an open case.

2. Pulmonary tuberculosis developed in juvenile diabetics, whose diabetes began at or before the age of twenty years, more than twelve times as frequently as among pupils in the Massachusetts grade and high schools.

3. Of 73 patients recovering from diabetic coma between February, 1929 and November, 1932, 13 have developed pulmonary tuberculosis within five years.

4. The incidence of pulmonary tuberculosis in adult diabetes does not show a decrease in rate corresponding with the general decrease in tuberculosis mortality in the community.

5. Pulmonary tuberculosis followed the onset of diabetes in 83 per cent of the cases.

6. In 126 autopsies upon diabetics with pulmonary tuberculosis, many healed foci, a tendency for the formation of tough, fibrous, pleural adhesions and a high frequency of caseating lesions with cavitation were outstanding features.

7. Chemical analysis of diabetic lungs showed strikingly lower concentrations of phospholipid and lipid than in nondiabetic patients.

8. The discovery of tuberculosis in the minimal stage is still rare but 7 new cases are reported.

9. The advantages of protamine-zinc-insulin in the treatment of tuberculous diabetics is discussed and dietary data are given.

10. Among 258 fatal cases the average duration of diabetes to death has increased from 5.4 years to 10.1 years and the duration of pulmonary tuberculosis from 2.7 years to 4.0 years.

11. Diabetic patients make excellent subjects for pneumothorax and thoracoplasty. Prognosis for the diabetic patients with pulmonary tuberculosis has been greatly improved by the introduction of insulin and can be still further enhanced by greater emphasis upon early diagnosis. The routine examination of every diabetic's chest by means of X-ray is recommended.

BIBLIOGRAPHY

(1) Quoted by BOULIN: Encyclopedia medico-chirugicale, Paris, 1936, section 10511, p. 2.
THIÉRY: J. A. M. A., 1935, *104*, 330.
THIÉRY: Diabète et tuberculose, Joure et Cie, Paris, 1934, pp. 7, 10.
(2) ROOT, H. F.: New England J. Med., January 4, 11, 18, 25, 1934, *210*, 1, 78, 127, 192.
(3) JOSLIN, E. P.: The present mortality of diabetic children, Ann. Int. Med., 1938, *11*, 1348.
(4) WIENER, J. J., AND KAVEE, J.: Am. Rev. Tuberc., 1936, *34*, 179.
(5) BROWN, L., AND SAMPSON, H. L.: J. A. M. A., 1932, *98*, 26.
(6) JORDAN, W. R., RANDALL, L. O., AND BLOOR, W. R.: Arch. Int. Med., 1935, *55*, 26.
(7) POPE, A. S.: A. M. A. Bull., 1937, *97*, 846.
(8) BERTRAM, E.: Zur Behandlung tuberkulöser Diabetiker, Ztschr. f. Tuberk., 1937, *78*, 13.
(9) SHERRILL, J. W., AND COPP, E. F. F.: Observations with protamine zinc insulin, clinical and experimental studies, Publication of Scripps Metabolic Clinic, La Jolla, San Diego, California, 1937.
(10) BOISSEVAIN, C. H., AND SCHULTZ, H. W.: A lipoid growth factor for the tubercle bacillus, Tr. Natl. Tuberc. A., 1938, p. 145.
(11) WOLFF, G.: Tuberculosis and civilization. Part II. Interpretation of the etiological factors in the epidemiology of tuberculosis, Human Biol., 1938, *10*, 251.
(12) FALLON, J. T.: Silicosis and pulmonary tuberculosis, Canad. M. A. J., 1937, *36*, 223.
(13) CAREY, H. U., AND HUNT, H. M.: Chemical nature of cataract in the diabetic, New England J. Med., 1935, *212*, 463.
WAITE, J. H., AND BEETHAM, W. P.: Visual mechanism in diabetes, Ibid., 1935, *212*, 367.
(14) HIMSWORTH, H. P.: Pulmonary tuberculosis complicating diabetes mellitus. Ouart. J. Med., 1938, *7*, 373.

ORAL TUBERCULOSIS[1]

JAMES CLUTE BRYANT

Tuberculous infection of the oral cavity does not appear to be as common as was formerly supposed. Observation of patients at Glen Lake Sanatorium, Oak Terrace, Minnesota, over a period of eighteen years, has disclosed 17 cases which are reviewed herewith.

The ulcerous processes have in all instances been secondary to a pulmonary condition. In most cases there has been an extensive involvement of the chest. Frequently there has been associated tuberculous spine, kidney, enteritis and rectal fistula. Tuberculous oral lesions have been seen for the most part in patients with a poor prognosis or in far advanced terminal cases.

It was thought at one time that tuberculous oral lesions were incurable. Some few lesions have healed however, but in most instances only when the patient's general condition showed improvement.

A tuberculous lesion of the oral cavity, like one of the vocal cords, is a persistent and chronic ulceration. If the patient has little or no resistance the lesion progresses steadily in the soft tissues. In two cases there was definite bone involvement. The bone surrounding the roots of a few teeth was gradually eroded, loosening the teeth and necessitating their removal.

Tuberculous lesions of the oral cavity have certain essential characteristics peculiar to themselves. They may occur singly or multiply. The mouth lesions of tuberculosis are presumed to appear first as small yellowish nodules which break down and ulcerate. The developed ulcer is a very painful open sore, especially so when the tongue is involved. Acidulous, salty, sweet and spicy foods prove irritating to the exposed nerve endings of the raw ulcer.

In describing a typical oral lesion, visualize a circular or irregular denuded area with a typically punched-out appearance, a millimetre or more in depth, situated in the tongue substance or the soft tissues of the oral cavity. The peripheral edge overhangs the denuded area

[1] From the Department of Oral Surgery, Glen Lake Sanatorium, Oak Terrace, Minnesota.

slightly. In reality the edge is being constantly undermined, increasing the size of the lesion. The tissue immediately adjacent to and circumscribing the tuberculous lesions presents a raised, swollen and inflamed appearance. This infiltrated area around the lesion is soft on palpation in contrast to the hard induration of cancer. The lesion may or may not be fissured. It will vary from a few millimetres in size to involvement of half the mandible and adjacent soft tissues. A thin pseudomembrane or plaque protects slightly the underlying raw muscle, nerves, blood vessels and other tissue. The lesion may vary from shades of light gray and dirty yellow to a gray violet. The violaceous color is due to the congested and cyanotic blood vessels laid bare by the lesion. The larger lesions of long standing are sometimes sprinkled with yellow granular tubercles. Slightly oozing ends of blood vessels give additional variation in color and design. These minute endings of eroded blood vessels give some lesions a speckled red or raspberry appearance.

In large denuded inactive areas, such as the oral pharynx, the lesions present an obvious pseudomembrane. The plaque in this location is usually grayish white. These lesions are not as painful as those on the motile tongue. Deep fissures sometimes form in tongue lesions which develop into finger-like protrusions, radiating out from the initial lesion. When the patient's resistance is low the protrusions become wider and wider and later coalesce until a huge lesion, irregular in outline, presents itself.

The findings of tubercle bacilli in smears from the lesions afford a positive diagnosis. Biopsy of the ulcer will give the characteristic picture of a tuberculous lesion.

Success in treatment of tuberculous oral lesions is almost always coincidental with the patient's faltering condition. If his general condition is improving, success may be met with in the treatment of the ulcer. Or if the active process of lung tissue destruction slows down, the oral lesions sometimes heal although the ultimate fate of the patient remains the same. If he is on a rapid down-grade, the infection in like manner continues to grow and spread. Patients have gone to postmortem examination with the greater portion of the tongue and soft tissues of the oral pharynx involved. In one exceptional instance, however, the patient's tongue lesion was completely healed at postmortem examination three months later. The exciting and aggravating cause of the ulcer here appeared to be broken teeth of an old denture. Follow-

ing construction of a new denture, the lesion completely healed. There was an unhealed tuberculous laryngitis.

In another instance the patient's small tongue lesions healed of their own accord despite a slow but insidious progression of his pulmonary tuberculosis.

To make a set rule as to the eventual outcome of a tuberculous involvement of the oral cavity would therefore be a fallacy. It is worthwhile to continue therapeutic endeavors despite the apparent hopelessness of the situation. The soothing effect on the patient's mind in knowing that everything possible is being done for him is certainly worth the time and effort involved.

Inasmuch as the patient with a tuberculous oral lesion is more frequently a terminal case and consequently too ill, weak and listless to use the simplest prophylactic measures, a terribly foul mouth presents tself. There are present excessive accumulations of hard calculus and soft food material with resulting inflamed gums. This foul condition of the mouth is favorable to and naturally tends to increase the progress of the lesion.

The tuberculous lesions occurred as follows: 9 of the tongue, 1 of the tongue and mandible, 2 of the hard palate, 1 of the hard and soft palate, 1 of the pharynx and soft palate, 1 of the soft palate, 1 of the maxilla and 1 of the mandible.

Two cases presented a history of lesions forming in tooth sockets developed before admission.

In approximately 11,366 extractions over an eighteen-year period on patients for the most part with an advanced stage of tuberculosis, no tuberculous ulcerations of the tooth sockets were noted.

In the consideration of this remarkable circumstance, one must be cognizant of the fact that as a rule only patients with a favorable prognosis are given the beneficial treatment resulting from the extraction or removal of oral foci of infection.

J. H., case 1630, an auto salesman, age 41 years, entered Glen Lake Sanatorium on December 15, 1924 with a diagnosis of laryngeal tuberculosis and pulmonary tuberculosis moderately advanced. Physical examination revealed signs of infiltration down to the second rib and fourth vertebral spine on the right and to the first interspace and third vertebral spine on the left. The epiglottis and false cords were swollen and oedematous and there was an ulcerated area present in the epiglottic pharyngeal sulcus. The cords were not

visualized but approximated well on phonation. Apparently the entire pharynx was oedematous. The X-ray report was bilateral fibroid pulmonary tuberculosis with cavity formation right upper lobe. His blood picture showed mild secondary anaemia.

He presented X-ray evidence as well as symptomatic evidence of tuberculous enteritis. He entered with a draining maxillary sinus which followed the extraction of the upper first molar in October, 1924 previous to admission. Four attempts to suture and close the opening met with failure and the sinus continued to drain.

His discharge diagnosis on December 24, 1925 was laryngeal tuberculosis, quiescent; pulmonary tuberculosis, arrested; tuberculous enteritis, apparently quiescent. He was advised to continue home treatment and particularly not to overexercise.

The patient was readmitted December 27, 1927. The left maxillary sinus was discharging a thick pus ranging from yellow to greenish-white in color. Six months previous to entering the Sanatorium the patient had the lower left first molar extracted. A small sinus remained which later developed into an ulcer. At the time of the patient's readmission it was 6 x 4 x 1 mm. in size. It was irregular in form with prominent edges which were undermined. The uneven granular floor of the ulcer was covered with a yellow pus. Pin points of blood were discernible. The ulcer was quite painful from contact with food material and the necessary work of mastication.

A biopsy taken in March showed definite tuberculosis. The laboratory report was as follows: Many well formed tubercles in submucosal tissue; some show caseous centres. There is an occasional tubercle in the mucosa. There is focal infiltration. The extravasated blood is probably traumatic.

The patient's general condition improved and, under daily treatment with lamp and mercurochrome, the ulcer had decreased to a little more than half size by June 5, 1928. The edges of the ulcer did not appear to be as markedly infiltrated and raised as they were previously and the surface had a better color with little secretion coming from its surface. There was only a small amount of pus from the region of the first molar above. An examination in December, 1928 showed the ulcer practically healed with the exception of a small area which had been the anterior portion of the ulcer. The presence of pus from the maxillary sinus could not be demonstrated. The patient's general condition was considered excellent and he was discharged March 20, 1929.

The patient was readmitted March 11, 1930 with a diagnosis of pulmonary tuberculosis; tuberculous ulceration of the left mandible; tuberculous ulceration about anus and tuberculous enteritis.

The left maxillary sinus was considered healed. The ulcer of the mandible was larger than at any previous time. The molars remaining had been

denuded and lost. The bony alveolar process supporting the second bicuspid was practically all absorbed leaving it loose and requiring extraction. The first bicuspid was also involved and later extracted. Two years later it was necessary to extract the almost completely denuded cuspid. The ulcer at this time, extended from the median line well back into the soft tissues anterior to the tonsil. The cheek was partly involved as were the tissues under the tongue on that side. The patient died April 14, 1932. At postmortem examination, the ulcer was seen to have involved more of the anterior teeth and the roof of the mouth showed whitish nodules.

E. M., case 4908, age 51 years, was admitted to Glen Lake Sanatorium on June 9, 1932 and died June 29, 1932. He had a diagnosis of extensive pulmonary tuberculosis, disseminated throughout both lungs and calcified hilum nodes on the left side. The sputum was positive. He had tuberculosis of the tongue and his prognosis was unfavorable.

The patient noticed white elevations scattered over his tongue in November, 1931. These recurred constantly and in January, 1932 he consulted a physician. At that time he was employed and felt well. The physician treated the lesions locally until March 10, 1932 with no visible improvement. At this time his three remaining upper molars were extracted. On March 20 he consulted another physician. At this time his tongue was furrowed but he suffered no systemic effects. Vincent's infection was diagnosed and he was unsuccessfully treated with neosalvarsan. He experienced loss of weight and physical weakness which prevented his working. In May he went to the Mayo Clinic. A biopsy of the lesion was done and a diagnosis of tuberculosis was made. He entered Minneapolis General Hospital on May 20 and was transferred to Glen Lake Sanatorium June 9, 1932.

The patient was in poor physical condition with atrophic muscles and pallid color, and he was dyspnoeic. He was unable to speak above a whisper. His tongue was markedly swollen and thickened so that it almost filled the mouth. There were nodules and ulcerations chiefly involving the left side. The lesions were covered with a dirty grayish exudate. The tongue was very painful and there was marked tenderness to the slightest touch. He died June 29, 1932.

P. Z., case 5100, a farmer, age 59, entered Glen Lake Sanatorium on October 23, 1934 with far advanced bilateral pulmonary tuberculosis with bilateral cavitation. The sputum was positive for tubercle bacilli. Two years previous to admission the patient had had a biopsy of the tongue made for a chronic ulceration of a year's standing, which had been diagnosed tuberculosis. A diagnosis of pulmonary tuberculosis was also made at that time.

The admission examination showed a marked depression on the left side

of the tongue about a half inch from the tip where the previous ulcer had been surgically removed. On the anterior surface of the tongue on the right side there was a new ulceration which was about one centimetre in diameter. The edges of the ulcer were irregular and its surface was covered with a membrane-like structure which was gray in color. The ulcer was quite painful and the tongue substance around the ulcer was inflamed and swollen. The patient was quite hoarse from the time he was admitted until his death. The soreness in his throat increased all the time and it became more and more difficult for him to swallow food or take liquid nourishment. The patient's lower teeth were sharp and abraded. He wore a full upper denture which was quite old and worn, some of the teeth being broken and sharp. This condition of his own lower teeth and those of the artificial upper tended to cut and irritate the tongue lesion. They might have been the initial cause. The abraded edges of the lower teeth were rounded and smoothed with stones and a new upper denture was constructed. Following this treatment, the tongue lesion gradually decreased in size and when the patient died two months later, it was completely healed.

The postmortem examination showed chronic pulmonary tuberculosis and tuberculosis of the larynx, spleen, kidney, epididymis, testicle, prostate and intestines.

R. S., case 825, a 34 year old barber, entered Glen Lake Sanatorium on August 3, 1921, with an advanced bilateral parenchymal tuberculosis. The sputum was positive for tubercle bacilli.

There was an ulcerated area on the inside of the lower lip extending from the right central incisor to the first bicuspid in width and from the free margin of the lip to the gum margin. The surface of the lesion was covered with tough, warty-like excrescences. There were two deep fissures in this area. There was quite a bit of infiltration about the area. There was a small superficial ulceration of more recent development below the lip margin, opposite the left central incisor. On the left side of the tongue opposite the first molar region, there was a prominence of the tongue where it bulged through the opening left by the missing tooth. On this prominence there was a small superficial tender ulceration about one-fourth inch in diameter. Biopsy examination showed tubercles.

The history of the tuberculous lesions was as follows: A year previous to admission, a sore spot was noticed on the left side of the tongue which was painful when eating. This area became firm, and then filled with pus which broke and an ulcer formed. Granulations formed on the bottom of the ulcer and it was healed ten months later; after five months it again became sore and ulcerated, remaining so ever since.

In October, 1920 a cold sore developed on his lower lip which healed. On

the edge of this area an ulcer developed the size of a dime which discharged pus continuously. Shortly after this, three small ulcers developed in the pharynx which were extremely painful on swallowing. The ulcers were treated with silver nitrate during the winter. In April, 1921 he learned he had pulmonary tuberculosis. During the spring and summer while curing, the ulcers were practically healed. In October, 1921, while curing at the State Sanatorium at Walker, Minnesota, the ulcers on lip and cheek again developed, ulcerating, spreading and discharging from then on. The patient left April 6, 1922 against advice and he died August 8, 1923.

In addition to these cases 13 other patients were observed. Their main oral lesions were distributed as follows: tongue 8, palate and uvula 1, soft palate 3, alveolar ridge 1. One of these patients was discharged as arrested, 2 are declining at the time of writing and the remaining 10 patients have died.

CONCLUSIONS

1. Tuberculous lesions of the oral cavity are comparatively rare, only 17 cases being detected in the oral examination of some 7,000 far advanced cases over a period of eighteen years.

2. Tuberculous tongue lesions frequently have a history of mechanical irritation from sharp edges of decayed and abraded teeth, broken silver fillings, gold inlays, crowns or broken artificial teeth. These sharp edges traumatize the tissue.

3. Constant irrigation and bathing of the oral tissues by the salivary and mucous secretions render the oral tissues highly resistant to tuberculous infection.

4. Tuberculosis of the oral cavity is a secondary manifestation of a far advanced pulmonary condition with an unfavorable prognosis.

5. Where the prognosis is favorable, tuberculous oral lesions are seldom formed in tooth sockets following extractions, despite the presence of heavily laden positive sputum.

BILATERAL TUBERCULOUS PLEURISY WITH EFFUSION[1]

An Analysis of Fourteen Cases

GEORGE C. WILSON

Bilateral pleurisy with effusion in tuberculous patients is generally little more serious than effusion on only one side, but occasionally it causes distressing and even alarming symptoms and the patient's life may depend on frequent aspiration of both pleural cavities. That such an alarming complication has received so little notice in the literature suggests its rarity.

Ameuille (1) in 1917 reported that tuberculosis of the serous cavities, and especially of the pleura, was strikingly frequent in soldiers of the French army. He said that multiple serous infections were most frequently seen in young patients, rarely in those over twenty-four years of age. The serous membranes were involved in 270 out of 2,600 tuberculous soldiers. Isolated pleuritis was the most frequent, but in an unstated number of cases the pericardium, peritoneum, meninges or synovial membranes were involved likewise or alone. He found that the lungs did not become involved often.

Als (2) first reported an instance of bilateral effusion in a pneumothorax patient. Fishberg (3) reported another a few months later and said that Forlanini in the treatment of hundreds of patients had never met with a case. Nor had Saugman. He also stated that Brauer and Spengler (4) had said there was no such case in the literature. Peters (5) in 1925 reported 3 cases and at that time could find 20 others in the literature. Peters thought that bilateral effusion indicated a bad prognosis. An occasional case of tuberculous polyserositis (6, 7) has been reported since. Howard and De Veer (8) have produced multiple serous effusions in tuberculous guinea pigs by repeated inoculations of small amounts of tuberculin.

A study of the patients with bilateral tuberculous pleurisy with effusion under observation in a sanatorium seems worth reporting. At Gaylord Farm Sanatorium from January 1, 1928 to January 1, 1938, 1,552 patients have been admitted with a diagnosis of tuberculosis.

[1] From The Gaylord Farm Sanatorium, Wallingford, Connecticut.

Fourteen patients with proved or probable tuberculosis developed bilateral pleuritis with effusion. In this group 5 were under twenty-five years of age; 5 were in their thirties and 4 were forty or more years of age. Youth seems not to be a factor in the development of this complication.

Nine patients were males and 5 were females. Five of the group were under pneumothorax treatment and one of these developed effusion first on the contralateral side.

Ten patients had pulmonary tuberculosis, 7 with definite involvement of both lungs. Three of these had tuberculous laryngitis also, and 2 had intestinal tuberculosis. There was pericardial involvement in 3 and peritonitis with ascites in another. The patient with the most extensive tuberculosis died three months after admission. Another had pleuritis with effusion and pericarditis develop as complications of empyema and spontaneous pneumothorax from which he died six months later. A third, who also had diabetes mellitus as well as far advanced tuberculosis, died of an embolus in the pulmonary artery after a long period of strict bed-rest. A fourth patient with far advanced pulmonary tuberculosis and intestinal tuberculosis made an uneventful recovery from bilateral pleurisy with effusion and pericarditis with effusion, but died in another hospital five years later after an exacerbation of his pulmonary tuberculosis. A fifth patient with tuberculosis in both lungs, spinal caries and tuberculosis of the knee is still bedridden seven years after resorption of bilateral effusion. A sixth patient developed acute glomerular nephritis shortly after resorption of bilateral effusion and while under treatment for bilateral pulmonary tuberculosis. He was transferred to a general hospital and has not been heard from since his discharge from there with chronic nephritis. A diagnosis of pericarditis was made at the general hospital but this may have been a complication of nephritis and not tuberculous. Two patients are working and the remaining 3 are showing satisfactory improvement under treatment. In these 10 patients bilateral pleurisy with effusion seems to have been an indication of the extent of the disease and in all of them it seems to have been the result of direct extension to the pleurae of underlying pulmonary tuberculosis.

Four patients with bilateral pleuritis with effusion had no demonstrable pulmonary involvement. One of these also had an effusion into a knee joint from which tubercle bacilli were isolated. He has been working for seven years. Another of the 4 has a tuberculous kidney

for which she is under treatment. A third developed iritis which was diagnosed as tuberculous. She was given frequent small doses of tuberculin subcutaneously before she developed bilateral pleuritis with a small effusion into each pleural cavity. Her family doctor also heard a pericardial friction rub at one time. Aspiration of pleural fluid was attempted without success. She had frequent unexplained blazes of fever. She was taken to another hospital where she died. A report has not been sent to us. The fourth patient in this group was the sixty-five year old housekeeper at the sanatorium. Shortly after the onset of bilateral pleuritis, she began having severe pains in most of her joints, together with swelling of the joints of the fingers and toes. The effusion into the pleural cavities was slight. Her recovery from the acute arthritis and pleuritis was uneventful and she has been working for seven years since in spite of her advanced age. She was not diagnosed as tuberculous but is included because she might be considered as belonging to the group of allergic polyserositis.

SUMMARY

1. Fourteen patients with bilateral pleuritis with effusion are reported.

2. Most of these patients developed pleuritis as a complication of extensive pulmonary tuberculosis and by direct extension from underlying disease to the pleura.

3. Four patients with no demonstrable pulmonary tuberculosis are included in the group. Two of these had tuberculosis elsewhere from which tubercle bacilli were isolated. In the other two, the tuberculous aetiology is doubtful.

REFERENCES

(1) Ameuille, P.: Tuberculose pleurale et tuberculose généralisée des séreuses, Ann. de méd., 1917, *4*, 55.

(2) Als, E.: Ein Fall von rechtsseitigem Pneumothorax Artificialis mit linksseitiger Pleuritis Exudativa, Ztschr. f. Tuberk., 1920, *21*, 333. Cited by Peters (5).

(3) Fishberg, M.: A case of artificial pneumothorax complicated by hydropneumothorax and pleurisy with effusion on the untreated side, Am. Rev. Tuberc., 1920, *4*, 649.

(4) Brauer and Spengler: Handbuch der Tuberculose, 1919, III, p. 227. Cited by Fishberg (3).

(5) Peters, A.: Contralateral exudative pleuritis complicating artificial pneumothorax, Am. Rev. Tuberc., 1925, *10*, 583.

(6) Burrell, L. S. T., and Hare, Dorothy C.: A case of tuberculous polyserositis with predominant pericardial involvement, Lancet, 1929, *217*, 1303.

(7) Swan, W. H., and Bortree, L. W.: Bilateral pleural effusion and mediastinitis, J. A. M. A., 1926, *87*, 2162.

(8) Howard, T., and De Veer, J. A.: Experimental tuberculous allergic serositis and its relationship to human polyserositis, Am. Rev. Tuberc., 1936, *33*, 755.

ERYTHROCYTE SEDIMENTATION[1,2]

Its Practical Value in the Management of Pulmonary Tuberculosis

THOMAS DE CECIO AND BENJAMIN J. ELWOOD

Within the past ten years, the erythrocyte sedimentation rate has been advanced to the rank of a valuable laboratory procedure to aid the clinician in better evaluating moot clinical problems. Particularly has the literature lauded the significance of this phenomenon in the field of tuberculosis. It is claimed that the sedimentation rate is not only a very sensitive index of activity in tuberculosis, but also reflects the clinical course of the process and yields significant prognostic data.

In putting into practice these observations, it was our frequent experience that results did not conform accurately with the findings of others. This study was therefore undertaken to determine whether the sedimentation rate offers any added information which cannot be gained clinically or gives further assurance to the clinical impression. A total of 825 consecutive admissions were studied. Of these, the initial rates were analyzed in all, while in 338 detailed analysis of the serial rates was made. The latter group had one determination on admission, routinely once a month while in the hospital and in the Out Patient Department, at the time of any clinical complication or anatomical change confirmed by X-ray examination and on discharge. The method employed was that described by Cutler (1), the technique of which is well known.

Throughout the entire study the evaluations as to type of lesion, activity, course and prognosis were based predominantly on changes revealed by X-ray examination, the clinical findings serving only to corroborate the impression thus gained.

EVALUATION OF ACTIVITY

The impression is prevalent that the sedimentation rate is a highly accurate index of activity in cases of pulmonary tuberculosis. In fact,

[1] Read before the Clinical Section of the New Jersey State Tuberculosis League, January 5, 1938.

[2] From the Hudson County Tuberculosis Hospital, Dr. B. S. Pollak, Medical Director, Jersey City, New Jersey.

the statement is made in the literature (2) that "a normal sedimentation test was never obtained in an individual unless he was healthy or the disease which he was harboring was of such nature that little or no destruction of tissue was taking place at the time the test was performed, —certainly not enough to disturb the natural stability of the blood." There is a formidable number of authors (Masten (3), Siltzbach (4), Kaminsky and Davidson (5), Friedman (6), Morriss (7), Levinson (8), Briskman (9), Volk (10), Cass and Sutermeister (11), Banyai and Anderson (12)) who are more or less in conformity with this concept. There are others (Luzzatto-Fegiz (13), Sticotti (14), Bochalli (15)), whose writings antedate many of the contributors mentioned above, who do not hold the test in so high a regard as an indicator of activity. Cutler's figures taken as representative of the former group, reveal that 87 per cent of clinically active cases have an elevated rate and that 97 per cent

TABLE 1

Correlation of initial sedimentation rate and activity

	NORMAL RATE	ELEVATED RATE	TOTALS
Active	138	530	668 (79% elevated)
Inactive	86	71	157 (55% normal)
Totals	224 (61% active)	601 (88% active)	825

of inactive cases present a normal rate. Our work (table 1) substantiates these findings in part, in that 79 per cent of the active cases presented an elevated rate but only 55 per cent of the inactive cases showed a normal rate. These figures are not at too great a variance with those of Cutler, Masten, Siltzbach, etc. But when one considers further that, out of 224 admissions with normal rates, 61 per cent presented active lesions, the significance of the sedimentation rate in the determination of activity immediately diminishes markedly.

Considering activity based on the sedimentation rate in comparison with anatomical activity alone (substantiated by subsequent course), it was found that exudative lesions were associated with an elevated rate in 73 per cent of the cases and that productive lesions were associated with an elevated rate in 77 per cent of the cases. These figures are in accord with the view expressed by Bochalli (15) that a differentiation between exudative and productive tuberculosis on the basis of the sedi-

mentation rate is not possible. Thus, the estimation of activity by determining the initial sedimentation rate is inconclusive.

COURSE OF DISEASE AND SEDIMENTATION RATE

Again the literature abounds with the writings of observers such as Cutler (16), Cass and Sutermeister (11), Spector and Muether (17), Friedman (6), Levinson (8), who feel that the sedimentation rate reflects accurately the course of the disease. On the other hand there are those, such as Voss (18), Sticotti (14), who, though concurring in the view just described, are wary of its accuracy.

In order to study this phase of the subject, the course of the disease was considered as "regressive," "mutative,"[3] "progressive," or "unchanged." These are not single observations but represent the trend of pathological change.

TABLE 2

Correlation of the anatomical course of 338 cases and their serial sedimentation rates

	TYPICAL	SOME SIGNIFICANCE	NO SIGNIFICANCE	TOTALS
Regressive	70	50	24	144
Mutative	39	35	5	79
Progressive	36	23	6	65
Unchanged	36	13	1	50
Totals	181(55%)	121(34%)	36(11%)	338

In 338 cases so studied (table 2) with serial rates it was found that in only 55 per cent did the sedimentation rate reflect the anatomical changes. Certainly, a clinical adjunct which is only 55 per cent accurate is not of great practical importance nor does it deserve, in our clinical armamentarium, so highly vaunted a place as the literature leads us to believe.

PROGNOSIS AND SEDIMENTATION RATE

The most interesting phase of this work was the comparison of the prognosis based on the sedimentation rate as against the clinical impression. In dealing with its prognostic significance in tuberculosis, the literature is rather extensive and one notes a fair diversity of opinion. There are those (Westergren (19), Siltzbach (4), Friedman (6), Roche

[3] "Mutative" refers to that characteristic of a lesion which for the period of observation demonstrated progression and regression either alternately or concurrently.

(20), Davies (21)) who highly praise its prognostic value, some even placing it above the clinical evaluation of a case; others (Frimodt-Moller and Barton (22), Heaf (23), Weichsel (24)) though agreeing that it is of some value are not wholly convinced and still others (Houghton (25), Beaumont and Dodds (26)) attach very little importance to the test prognostically.

For comparative study a group of 182 patients, who were clinically and anatomically stable for at least three to six months before discharge, was analyzed. They divided themselves on leaving the hospital into two subgroups, those with elevated rates and those with normal rates. The study was continued without interruption in the Out Patient Department for a period varying from six months to five years (80 per cent for one year or more).

TABLE 3

Analysis of sedimentation rates of discharged cases observed from six months to five years

ELEVATED RATE ON DISCHARGE				NORMAL RATE ON DISCHARGE			
Reactivated		Unchanged		Reactivated		Unchanged	
After Rate Normal	While Rate Still Elevated	Rate Dropped to Normal	Rate Still Elevated	While Rate Normal	Rate Elevated Before or After	Rate Normal	Rate Became Elevated
3	17	39	69	7	6	39	2
20(16%)		108(84%)		13(24%)		41(76%)	
128				54			

It is interesting to note that of those discharged with an elevated rate (128), 108, or 84 per cent, remained well for six months to five years and that 50 per cent were still elevated after one to five years' observation. Of the 20 (16 per cent) that reactivated, 17 did so while the rate was still elevated. Of the group discharged with normal rates (54), 41, or 76 per cent, remained well over a period of one to five years, while 13 (24 per cent) reactivated during the period of observation. Seven of the 13 reactivated while the rate remained normal. Certainly, the group with elevated rates on discharge fared just as well as the one with normal rates (table 3).

Thus prognostically, the impression gained from a meticulous clinical and X-ray evaluation was by far more practical and more accurate than that deduced from the sedimentation rate, for out of a total of 182 cases eligible for discharge on a clinical and X-ray basis only 54 would have

been eligible on the basis of the sedimentation rate, with just as much chance for relapse as those with elevated rates.

DISCUSSION

Realizing that, despite the findings presented, the sedimentation rate, perhaps in a modified form, might still reveal valuable information, accessory studies were undertaken. The first factor to be considered was that of the rôle of anaemia. The observations of Friedman (6) would indicate that correction for anaemia is essential, whereas Siltzbach (4) showed that in the majority of instances anaemia played an insignificant part. It was our impression that if corrections were made less conformity than already noted would be obtained. The more recent work of Cutler (27) substantiates our impression and proves conclusively that correction more often than not leads to erroneous results.

The second point considered was the actual curve or graph. Eliminating the phase of cell packing, and considering only the phase of cell aggregation and precipitation, no greater conformity or significance could be discerned, a fact which might well have been anticipated since the latter two phases are reflected in the sedimentation index. An attempt was even made at evaluation of the rate of change of sedimentation per five minute periods but no significant results were obtained.

It is important to note at this point the work of Patterson (28), who found a significantly low sedimentation index (1 to 7, average 3.5) for normal individuals. His findings lead one to feel that the accepted normal indices are too high. Patterson showed that, in 41 release cases with active tuberculosis, the average index was 8.1 and that in another group comprised of 65 active cases with multiple determinations the average index was 9.5. Perhaps a reconsideration of the normal standards is in order?

SUMMARY AND CONCLUSIONS

The study of the sedimentation rate with a view to establishing its practical value in the management of tuberculosis of the lungs reveals that:

1. In the initial study of a case, the occurrence of an elevated rate indicates in a considerable majority of instances the presence of an active lesion. However, the presence of a normal rate does not exclude an active lesion.

2. In the correlation of serial rates with definite pathological trends,

the case percentage (55 per cent) of compliance of the rates with the anatomical course is not of sufficient significance to be of practical value.

3. No greater percentage of relapse or reactivation occurred in the group discharged with elevated rates than in the one with normal rates. And furthermore a considerable majority of those patients with sustained elevation of the sedimentation rate have remained well from one to five years.

4. The information obtained from the clinico-pathological study not only reveals all but more information than can be gleaned from sedimentation rates alone and with a greater degree of accuracy.

Thus the use of the sedimentation rate in the management of pulmonary tuberculosis as a criterion of activity, course and prognosis is not of sufficient clinical value to be essential in the care of the tuberculous.

Deep appreciation is herewith expressed to Dr. B. S. Pollak whose indulgence and encouragement made possible this work and to Dr. B. P. Potter whose stimulus and guidance played an inestimable rôle in the actual studies.

REFERENCES

(1) Cutler, J. W.: Am. J. M. Sc., 1932, *183*, 643.
(2) Cutler, J. W.: Am. Rev. Tuberc., 1930, *21*, 347.
(3) Masten, A. R.: Ibid., 1934, *29*, 690.
(4) Siltzbach, L. E.: Ibid., 1934, *29*, 673.
(5) Kaminsky, J., and Davidson, D. L.: Ibid., 1932, *26*, 282.
(6) Friedman, S.: Ibid., 1934, *29*, 198.
(7) Morriss, W. H.: Ibid., 1924, *10*, 431.
(8) Levinson, S. A.: Ibid., 1923, *7*, 264.
(9) Briskman, A. L.: Ibid., 1930, *22*, 562.
(10) Volk, R.: Ibid., 1937, *36*, 567.
(11) Cass, J. W., Jr., and Sutermeister, M.: New England J. Med., 1934, *209*, 252.
(12) Banyai, A. L., and Anderson, S. V.: Arch. Int. Med., 1930, *46*, 787.
(13) Luzzatto-Fegiz, G.: Tubercolosi, 1927, *19*, 196.
(14) Sticotti, S.: Ibid., 1927, *19*, 331.
(15) Bochalli: Ztschr. f. Tuberk., 1928, *40*, 274.
(16) Cutler, J. W.: Am. Rev. Tuberc., 1932, *26*, 134.
(17) Spector, H. I., and Muether, R. O.: Ibid., 1932, *25*, 533.
(18) Voss, H.: Ztschr. f. Tuberk., 1930, *60*, 431.
(19) Westergren, A.: Acta med. Scandinav., 1920, *54*, 247.
(20) Roche, H.: Brit. M. J., 1937, *2*, 466.
(21) Davies, G. I.: Tubercle, 1930, *11*, 450.
(22) Frimodt-Moller, C., and Barton, R. M.: Ibid., 1933, *14*, 529.
(23) Heaf, F. R. S.: Ibid., 1926, *8*, 97.
(24) Weichsel, J.: Deutsche med. Wchnschr., 1924, *50*, 1603.
(25) Houghton, L. E.: Tubercle, 1935, *17*, 48.
(26) Beaumont, G. E., and Dodds, E. C.: Recent advances in medicine, Blakiston, Churchill, 1934.
(27) Cutler, J. W.: Am. J. M. Sc., 1938, *195*, 734.
(28) Patterson, H. A.: Am. Rev. Tuberc., 1936, *34*, 164.

THE EPIDEMIOLOGICAL ASPECTS OF THE NEGATIVE TUBERCULIN REACTION[1]

M. PARETZKY

The problem of the significance of primary infection in the immunology of tuberculosis has retained its interest up to the present time. The divergence of opinion among the investigators of the subject has added interest to this problem. As this problem can be satisfactorily solved only on the basis of facts, we feel that presentation of some material accumulated by us from observations on cases seen in the Chest Clinics of the Los Angeles County Health Department would be of some interest. It is our opinion that, in view of the fact that different negative reactors possess different immunity to tuberculosis, they should be accordingly divided into several different groups. In this paper we have divided them into four groups:

1: Persistently negative reactors possessing high specific immunity
2: Reactors previously sensitive to tuberculin, with a subsequent complete desensitization
3: Negative reactors with low immunity
4: Negative reactors subsequently becoming positive without developing the disease

In all studied cases the intracutaneous tuberculin (Mantoux) test was used.

GROUP 1. PERSISTENTLY NEGATIVE REACTORS POSSESSING HIGH SPECIFIC IMMUNITY

The existence of reactors of this type has been known since the early days of tuberculin testing. It must be borne in mind that some of the persistently negative reactors possibly are desensitized formerly positive reactors with the positive phase of the tuberculin record remaining undiscovered due to the late initial tuberculin testing. However, beyond doubt, many persistently negative reactors never were tuberculin sensitive. As an illustration we wish to cite the following case.

[1] From the Chest Division of the Los Angeles County Health Department, Los Angeles, California.

Case 1: A little Mexican girl had a series of negative tuberculin reactions. She was first tested with a dose of 0.1 mg. at the age of nine months. During a period of four years, 9 applications of Old Tuberculin, including the doses of 1.0 and 10.0 mg., were done. During this period of time she was exposed to two relatives with active pulmonary tuberculosis. A third relative, formerly an arrested case, had broken down with active tuberculosis and had to be institutionalized. Due to the early age at which the initial negative tuberculin test was observed, it is certain that this child could not possibly have burned out her allergy if such had previously existed. It is also certain that she possessed an immunity of a remarkably high potency.

Obviously this is the most desirable type of "contacts" with immunity functioning at highest level possible, sufficient to protect not only from the disease, but from the implantation of infection as well. Therefore, negative reactors of this type warrant a detailed study. We have made observations on 90 patients of this type, all of whom were negative to all doses of tuberculin applied, including in each instance the dose of 10.0 mg. In many cases the dose of 10.0 mg. was repeatedly applied.

There were 52 females and 38 males among this group, or 57.7 and 42.2 per cent respectively. The age distribution was: up to 4 years, 23, or 25.5 per cent; 5 to 9 years, 30, or 33.3 per cent; 10 to 14 years, 24, or 26.6 per cent; 15 to 19 years, 8, or 8.8 per cent; 19 years and older, 5, or 5.5 per cent. The 90 reactors belonged to 46 families. The distribution per family was: one to a family in 25 familes; 2 to a family in 9 families; 3 to a family in 7 families; 4 to a family in 3 families; 5 to a family, and 9 to a family in one family each. The average was approximately 2 cases to a family. This makes it suggestive that the factor of hereditary immunity has played an important part in the phenomenon studied.

Of course, all these 90 patients were diagnosed as nontuberculous on initial examination. On follow-up, 84, or 93.3 per cent, remained tuberculin-negative; 4, or 4.4 per cent, became positive reactors with negative clinical and roentgenological findings. Of these, one belonged to a family with a total of 5 negative reactors, 4 of which remained tuberculin-negative. This case was considered as indicative of the fact, frequently observed by us, that the evolution of the tuberculin record in cases of this type is often influenced by individual changes in the level of immunity. Three of the cases that eventually acquired tuberculoallergy belonged to families with one negative reactor in each. Two patients of this group, or 2.2 per cent, developed tuberculosis of the childhood

type; one soon became arrested. These 2 patients were members of the same family. We feel that a brief report of this family will be of interest.

Case 2: These 2 patients, Mexican girls, born in 1924 and in 1933 respectively, had an uninterrupted negative tuberculin record from January, 1935 to July, 1936. Four different tuberculin tests were made in the older girl during this period of time and six in the younger one. One dose of 10.0 mg. of Old Tuberculin was used in each case. At that time they were exposed to the mother who was diagnosed in December, 1934 as having active minimal pulmonary tuberculosis, and was pronounced arrested in August, 1936. A sister of these girls with moderately advanced pulmonary tuberculosis was placed in a sanatorium. She left it without permission in May, 1936, returned home and stayed there till June 8, 1936, on which date she returned to the sanatorium under compulsion. She died a few months later. As stated before, the two girls remained tuberculin-negative as late as July, 1936; a dose of 1.0 mg. of Old Tuberculin was applied to each of them at that time. In November, 1936 the girls had positive reactions to 0.1 mg. of Old Tuberculin. X-ray films taken then showed that the older of these girls had developed calcified tracheobronchial tuberculosis, and the younger hilar and parenchymal active tuberculosis of the childhood type. A follow-up film taken of the second case in May, 1937 showed only a slight decrease of the hilar shadows in both lungs.

The circumstances under which these two girls developed clinical tuberculosis are of interest. Some conclusions can perhaps be deduced from these cases. One is that negative reactors of this type, as a rule, endowed with high immunity, are liable to succumb to infection if a sudden increase of the dosage of infection to which they are exposed takes place. In other words, immunity even of the highest type is only relative and apparently limited to a certain dosage of infection and does not function beyond this limit.

Another conclusion confirming an old observation is that, in order to function efficiently, immunity apparently requires a more or less frequently repeating impact of infection of a certain potency. When this impact ceases or diminishes in its potency, immunity is likely to decline. Indeed, in the cited cases, both girls were tuberculin-negative though exposed to infection derived from two spreaders, their mother and sister. Later the mother became arrested and the sister was hospitalized. The dosage of infection to which the girls were subjected had decreased and perhaps even had come down to zero. Consequently, the girls appar-

ently lost a great deal of the previously existing immunity and, when their sister returned home for a few weeks only, they, being suddenly reëxposed to a potent infection, developed tuberculosis.

As it was stated before, 84, or 93.3 per cent, of the observed negative reactors of this group remained tuberculin-negative.

In view of the evidently persistently high immunity of these 90 individuals, it would be of interest to analyze the features of infection to which they were exposed. Among them there were exposed to one case of active tracheobronchial tuberculosis and one case of minimal pulmonary tuberculosis arrested at the same time, 1 case, or 1.1 per cent; to minimal pulmonary tuberculosis arrested 5 cases, or 5.6 per cent; to minimal pulmonary tuberculosis active, 22 cases, or 24.4 per cent; to moderately advanced pulmonary tuberculosis active, 29 cases, or 32.2 per cent; to far advanced pulmonary tuberculosis, 12 cases, or 13.3 per cent; to more than one case of active pulmonary tuberculosis at the same time, 20, or 22.2 per cent; to silicotuberculosis, 1 case, or 1.1 per cent. Altogether 61 negative reactors, or 67.8 per cent, were exposed to advanced cases of pulmonary tuberculosis.

The progress of the infecting cases could serve as another criterion of the degree of infection to which the 90 negative reactors were subjected. Of the 57 infecting cases, 1, or 1.8 per cent, was eventually cured; 11, or 19.3 per cent became arrested; 14, or 23.6 per cent, improved; 15, or 26.3 per cent, remained stationary; 8, or 14.0 per cent, became worse; 6, or 11.6 per cent, died. In 2 cases, or 3.5 per cent, there was no information as to the progress. It is of interest that in a fourth of the infecting cases there was a definitely unfavorable progress of the disease.

Eighteen, or 20 per cent, of the persistently negative reactors were exposed to 9 infecting cases with sputum occasionally positive for acid-fast bacilli. It is worth mentioning that 9 of these reactors belonged to two families, 4 and 5 respectively to a family. Again 18, or 20 per cent, of the persistently negative reactors were exposed to 7 infecting cases with sputum constantly positive for acid-fast bacilli; 13 of these reactors belonged to two families, 4 and 9 respectively to a family. Altogether, 36, or 40 per cent, of the total were exposed to cases with positive sputum, or, in other words, to considerable doses of infection.

The nature of exposure was constant and prolonged in 50 negative reactors, or, in 55.6 per cent of the total; constant but short in 10 cases, or in 11.1 per cent; almost constant in 10 cases, or in 11.1 per cent; with considerable interruptions in 16 cases, or in 17.8 per cent; occasionally in

3 cases, or in 3.3 per cent; there was no information in 1 case, or in 1.1 per cent.

The analysis of different phases of infection to which the 90 persistently negative reactors were exposed has brought out the significant fact that on the whole we have dealt with a group exposed to infection of considerable dosage and virulence.

We feel that, for the sake of comparison, other "contacts," which belonged to the same families as the reported 90 individuals, ought to be studied. Of the 46 families under consideration, in 4 families there were no other "contacts;" in 42 families there were 135 other "contacts;" of them 85 were positive tuberculin reactors on initial testing; 50 were negative tuberculin reactors.

The initial diagnosis of the positive reactors was as follows: tuberculosis of childhood type arrested, 9; tracheobronchial tuberculosis active, which later became arrested, 1; minimal pulmonary tuberculosis arrested, 1; nontuberculous, 68. On reëxaminations there were discovered among the positive nontuberculous reactors 2 cases with slight calcification; 2 others developed active childhood type tuberculosis; both of these cases became soon arrested.

The 50 negative tuberculin reactors mentioned above were not tested with high doses of Old Tuberculin. The dose of 10.0 mg. was not applied to any of the 50 individuals. Therefore it was deemed proper not to include them in the group of the 90 persistently negative reactors to all of whom the dose of 10.0 mg. of Old Tuberculin was applied, but to study them as a separate group.

On retesting, 20 of them had become positive reactors and one of these had developed slight pulmonary calcified lesions. Thirty negative reactors of this group have not changed their negative response to tuberculin.

GROUP 2. REACTORS PREVIOUSLY SENSITIVE TO TUBERCULIN WITH A SUBSEQUENT COMPLETE DESENSITIZATION

Some tuberculin-positive individuals manifest a tendency to a more or less complete spontaneous desensitization. We have reported (1) observations on 80 cases of this type, with a definitely established previous tuberculin record, which have in the course of time lost their specific hypersensitiveness to the extent that they failed to react to 10.0 mg. of Old Tuberculin. At present we shall limit ourselves to a brief reiteration of some of the immunological observations related to the subject of this paper.

Many of the 80 cases were exposed to considerable doses of repeated reinfection, the virulence of which was confirmed by the relatively frequent occurrence of positive sputum and of eventual death among the spreaders of infection. Some new cases of active tuberculosis have developed in the families exposed to the same infecting cases. Under these circumstances the fact of disappearance of hypersensitiveness in these 80 subjects, combined with the clinically observed complete freedom from disease among 80 per cent of these cases, testifies to the high level of immunity in these subjects. While in the majority of the studied cases of this group this phenomenon was purely an individual one, being limited to one member of the family only, there was ample evidence that in some other instances hereditary immunity was a powerful factor of desensitization. A tendency to reappearance of specific hypersensitiveness was observed in some of these cases. Nevertheless, densensitization has remained unimpaired in two-thirds of these cases at the time they were first reported by us. It is self-evident that one cannot speak of this group as of one consisting of genuine and persistent negative reactors as all of them had a previous positive tuberculin record. One cannot contend that the comparatively high level of immunity observed in these cases was due primarily to their total freedom from infection in the later period of their tuberculin record, as manifested by a negative reaction to 10.0 mg. of Old Tuberculin. Just the reverse, we can visualize how primary infection was implanted in these subjects and how the mechanism of inherent individual immunity which was not sufficiently potent to prevent this implantation was brought into powerful action by this infection, and, at the following stage of this struggle against infection, it was successful in achieving a gradual but complete elimination of infection. In other words, there is ground to believe that the high level of immunity in these cases was originally due to the positive phase of their tuberculin record. One wonders how many cases that are persistently tuberculin-negative over a long period of time are actually of this type, the positive phase of their tuberculin record remaining unknown because they were first tested after their specific hypersensitiveness had already completely disappeared.

Additional observations were made by us after these cases were first reported. We feel that some of them are of sufficient immunological interest to warrant a further report.

Case 3: A Mexican girl, born in 1927, had an initial positive tuberculin reaction with a negative X-ray film in 1931 and a series of negative reactions to

different doses of Old Tuberculin including several of 10.0 mg., from 1933 to 1936. She was exposed to the mother, who had minimal pulmonary tuberculosis with a practically stationary course of disease from 1931 to 1936. By the end of 1936 the mother took a sudden and rapid change for the worse. She was placed in a sanatorium and died there in March, 1937. In April, 1937 the daughter had a three-plus reaction to 0.1 mg. of Old Tuberculin and the X-ray film showed evidence of active tracheobronchial tuberculosis.

Case 4: Two white twin sisters, born in 1929, had an identical tuberculin record from 1930 to 1936, starting with a negative tuberculin reaction in 1930. In 1933 they both had positive reactions to 0.01 mg. of Old Tuberculin. In 1934 they had again negative reactions to 0.1 mg. of Old Tuberculin. During the following two years they had a series of negative reactions to different doses of Old Tuberculin including several doses of 10.0 mg. In May, 1936 one of the twins had an attack of measles. Tested again August, 1936 she had a three-plus reaction to 0.1 mg. of Old Tuberculin. The X-ray film revealed a large irregular area of increased density at the left hilum extending into the midlung field which was diagnosed as primary pulmonary and tracheobronchial tuberculosis. The other twin sister escaped the attack of measles and in August, 1936 had remained negative to a dose of 1.0 mg. of Old Tuberculin. The twins were intermittently exposed for a number of years to their father who had far advanced pulmonary tuberculosis with sputum positive for acid-fast bacilli. During the spring and summer of 1936 the father stayed at home.

These two cases are of interest inasmuch as they stress the epidemiological importance of two major factors. In the first case the factor responsible for the defeat of immunity which demonstrated its high efficiency over a period of years was exogenous infection. Immunity was successful in checking and subsequently completely eliminating the primary infection to the extent that even the dose of 10.0 mg. of Old Tuberculin failed to produce a reaction, but apparently it was not sufficiently potent to resist the increased doses of reinfection emanating from the infecting case shortly before death.

The second case demonstrated the importance of sustaining the potency of immunity on a certain level, which apparently is another essential epidemiological factor. Immunity was efficient previously in protecting the patient against the implanted primary infection; but when its level was lowered by an attack of measles the exogenous infection was victorious. It is of significance that the "control" case, the other twin sister who avoided measles, succeeded in maintaining her immunity on the previous effective level.

GROUP 3. NEGATIVE TUBERCULIN REACTORS WITH LOW IMMUNITY

In a previous report (2) we have presented findings on 46 previously negative reactors which later yielded evidence of tuberculous disease, both active and arrested. Since the publication of this report we have collected another series of 24 cases of the same type. Inasmuch as a detailed analysis of the conditions under which the 46 negative reactors of this type developed clinical tuberculosis was given in the previous report (2), we shall discuss at present only some of the most important facts elicited during the study of the additional cases.

Of the 24 primarily negative reactors of this group, 7, or 29.1 per cent, were whites; 16, or 66.6 per cent, Mexicans; 1, or 4.1 per cent, Cuban. Fourteen, or 58.3 per cent, were females; 10, or 41.6 per cent, males. Fourteen, or 58.3 per cent, were children up to 14 years; 10, or 41.6 per cent, above 14 years.

In one family there were 3 cases of this type; in another family, 2 cases; in 19 families there was 1 case in each.

The diagnoses and prognoses, after clinical tuberculosis became evident, were as follows: childhood tuberculosis arrested, 7 cases, all remained stationary; childhood tuberculosis active, 8 cases, with a very favorable progress in all: of them, 4 became arrested, 2 showed a complete and 2 a partial absorption of the lesions; minimal pulmonary tuberculosis active, 6 cases, of which 3 became arrested, 1 clinically improved, 2 remained stationary and were placed in a sanatorium; moderately advanced pulmonary tuberculosis with a cavity, 1, there was no further information about the progress of this case; far advanced pulmonary and miliary tuberculosis, 1 of each, both died.

We feel that it would be of interest to compare the exposure to infection of this group totalling 70 patients in both series, previously reported and recently collected, characterized by low immunity, with the 90 patients of group 1 with high immunity. We wish to repeat once more that both these groups consisted of primarily negative reactors with a widely divergent consequent clinical course.

Several different criteria were used in this comparison: (*a*) the type and stage of the disease in the infecting cases, (*b*) the percentage of cases with sputum positive for acid-fast bacilli on direct smear, (*c*) the percentage of eventual deaths, (*d*) the length of exposure. Not wishing to encumber this paper with statistical details we shall only state that the reactors of group 3, those that eventually developed tuberculosis, were as a whole exposed to somewhat larger doses of infection than the re-

actors of group 1, those that as a rule have remained persistently negative to high doses of tuberculin. Nevertheless, this slight excess of infection does not in our opinion explain the tremendous difference in the ultimate fate of the respective exposed reactors. Apparently the difference in the individual immunity was by far the greater factor. This observation is indirectly confirmed by the well known fact that in certain instances some members of the same families develop active tuberculosis while others, though exposed to the same infection, persistently fail to react to tuberculin.

GROUP 4. NEGATIVE REACTORS SUBSEQUENTLY BECOMING POSITIVE AND REMAINING IMMUNE

It is a common experience that many individuals, for some time negative to tuberculin, eventually acquire a positive reaction without developing any clinical or roentgenological evidence of tuberculous disease. One is tempted to assume that apparently their inherent immunity during the negative phase of their tuberculin record previous to the implantation of primary infection suffices to prevent such implantation for a certain length of time and later, when the implantation of infection takes place, the inherent and the added acquired immunity are potent enough to localize the attacking microörganisms and to protect the host against the development of active disease. We must keep in mind that at one time all known positive reactors were negative and that the negative phase of their tuberculin record has remained unknown due to a certain timing of the application of the tuberculin test. In this sense, then, most of the known positive reactors belong to group 4. Inasmuch as the known negative phase of the tuberculin record of the individuals of this group is of a secondary epidemiological importance to the positive phase, we shall limit our present discussion to the above short statement. We hope to have an opportunity to report in the near future some material pertaining to the positive phase of the tuberculin record of this group.

DISCUSSION

The classification of the negative tuberculin reactors used in this paper was devised for the study of our material only. We do not suggest it as a basis for classification of the negative tuberculin reactors in general.

For reasons just stated, group 4—the negative reactors that later became positive—was not studied in detail in this paper.

It seems that the main interest in the study of the negative reactors

is centred around the first three groups. Facts pertaining to each of these groups were brought out in the respective parts of the paper. We wish to discuss here briefly some epidemiological phenomena generally observed during the study of negative tuberculin reactors and applicable in varying degrees to the three first groups.

It seems that it is essential for the potency of immunity to be sustained on a certain level. If this level is lowered by various factors, among which intercurrent infections play an important rôle, disease may develop. However, in many instances the newly implanted tuberculous infection brings into action the reserve forces of immunity which are sufficiently potent to prevent the development of the disease and in some cases even to eradicate the invading infection after it succeeded to penetrate into the tissues of the host. This is manifested by the cycle in which specific skin hypersensitiveness moves in certain cases, from a negative tuberculin reaction to positive and back again to negative. This feature of relativity of immunity is also evident with regard to the dosage of infection. It seems that the efficiency of immunity in each individual case is apparently limited to a certain dosage of infection and does not function beyond this limit. In practice it is impossible to determine this limit, obviously because there is no way to measure more or less exactly the dosage of infection and especially the degree of immunity. We know only that this level is individually different. We may also surmise that this level is highly dependent on the amount of the reserve forces of immunity which can be developed by the host under the attack of the increased infection. It seems that efficient function of immunity depends in some cases on the frequency and regularity of the exposure to infection. Immunity may function efficiently in the presence of exposure but may become dormant later when the exposure either ceases completely or decreases, so that when the host is suddenly exposed again to a potent dose of infection there is not enough time to bring into action all the reserve forces of immunity, and disease may develop.

As it can be seen, the study of the function of immunity under varied conditions invariably brings to the front the problem of its reserve forces.

It is true that disease cannot develop in the absence of infection. The dosage of infection, its virulence, frequency, the intimacy and regularity of exposure are factors of paramount epidemiological importance. Nevertheless, in evaluating the rôle of all factors involved in the development of the disease, it seems that in many instances the factor of immunity is of greater epidemiological significance than the factor of infection.

One may say that the ultimate fate of the individual exposed to infection depends on factors working rather within than without his own body. This observation can also be interpreted in the sense that there is a very wide divergence in individual resistance.

It seems to us that conclusions derived from this study should not be considered as limited to negative tuberculin reactors. We hope to report later findings on positive reactors supporting this opinion. However, all these conclusions are brought to light much more clearly in the study of the response of the negative tuberculin reactors to exogenous infection than of that of positive reactors because of the more conspicuous changes in the tuberculin record, especially when these changes are correlated with the clinical picture.

As we have seen, the different types of negative tuberculin reactors vary in the potency of immunity possessed by them. In practice it is impossible to foretell to which group an individual negative tuberculin reactor will eventually belong.

Only time will reveal whether this reactor will remain well, uninfected or will succumb to disease. We still lack a reliable immunity test which could be helpful in the practical epidemiological field work. Therefore, in our opinion it behooves the field worker to watch very carefully all negative tuberculin reactors as potentially belonging to group 3 and thus susceptible to disease till in time a sufficient proof to the contrary will be accumulated.

It seems to us that, in the absence of a specific test for immunity in tuberculosis, a careful coördination of data derived from the epidemiological studies of the spreaders of infection and from the tuberculin and clinical records of the exposed "contacts" would be valuable in determining the degree of immunity possessed by these contacts. Naturally, to be of value the clinical and tuberculin records must contain data accumulated over a reasonable length of time.

In conclusion we wish to state that we realize fully that many important epidemiological problems in tuberculosis are far from being clearly understood. We are aware of the great differences in opinion on this subject existing among workers in the field of tuberculosis. Therefore, the opinions expressed by us in this paper are presented here only as personal impressions based on the accumulated reported material. We feel that presentation of such observations of facts and of personal opinions may be of some value as material for further studies and discussions.

SUMMARY AND CONCLUSIONS

For convenience of study, the negative tuberculin reactors were divided into four epidemiological groups:

1: Persistently negative reactors with high immunity
2: Negative reactors with a record of spontaneous desensitization following a period of tuberculoallergy
3: Negative reactors with low immunity
4: Negative reactors later acquiring tuberculoallergy and possessing adequate immunity during both phases of their tuberculin record

The opinion was expressed that immunity varies greatly in each of the above groups, that at best it is relative and that its efficiency depends on many exogenous and endogenous factors, among which exposure to tuberculous infection is of a great importance. It seems that, in general, successful resistance to disease depends a great deal more on the function of specific immunity than on the degree of exposure to infection.

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REFERENCES

(1) PARETZKY, M.: The disappearance of specific skin hypersensitiveness in tuberculosis, Am. Rev. Tuberc., 1936, *33*, 370.
(2) PARETZKY, M.: The intracutaneous (Mantoux) tuberculin reaction, A comparative study of positive and negative reactors, Ibid., 1935, *31*, 553.

THE DETECTION OF TUBERCULOSIS IN GROUP SURVEYS

PHILLIP T. KNIES[1]

There is, of course, no question of the fact that for maximum accuracy in the detection of tuberculosis every possible diagnostic procedure should be available. Such an ideal, however, is at present impractical of attainment in the examination of large groups of individuals. General expense, the lack of adequate physical equipment, and often of trained personnel, are potent limiting factors in such work despite the value and necessity of multiple procedures in selected individual cases. In cognizance of these facts several plans of survey have been suggested (1, 8, 13, 14, 10), each representing some compromise between expense and efficiency, but best calculated in the opinions of their respective proponents to serve in the detection of significant disease. The truly superior procedure has not yet been identified, for many considerations in the interpretation of data so obtained remain yet in the theory of tuberculosis pathogenesis and immunology. Continuation of methods emphasizing immunological reactions on the one hand, and radiological findings on the other is desirable as a means of critical evaluation of each (9).

Probably the routine most widely used in this country consists in a preliminary "screening" of suspects, particularly children, adolescents and young adults by tuberculin testing, followed by roentgen examination of only the positive reactors. In spite of valuable information, particularly of an epidemiological character, obtained in this way, it has appeared to the author that this procedure involves an inherent error of considerable magnitude, in that certain cases negative to tuberculin may yet show findings significant of tuberculous infection by roentgen examination. Such error has been admitted by advocates of this routine of mass examination for tuberculosis, but has been considered of insignificant proportion (8, 11). In the author's experience, however, the number of such instances occurring in a clinic[2] where both methods of examination were routinely applied appeared impressive, and the present study was

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undertaken to determine the degree of error which might be avoided by such combined examination in contrast with the findings of either method alone.

Two groups of individuals are included in the present study. The first consists of 206 persons, ranging in age from five to seventy-five years, otherwise unselected except that they were consecutive cases showing X-ray findings significant of tuberculous infection. Usually such findings comprised calcification at the hilum, or in the parenchyma, or both, though there was occasionally included a patient with frankly exudative pulmonary infiltration, but none with involvement beyond minimal, and none with cavitation. These exclusions were observed in an effort to

TABLE 1*

Results of tuberculin testing by intracutaneous use of OT in 206 cases showing radioscopic evidence of tuberculous infection, subgrouped according to age

AGE	FIRST TESTS	NEGATIVE	+	++	+++	++++	CASES LOST	SECOND TESTS	NEGATIVE	+	++	+++	++++
0–5	4	2	2				2						
6–10	22	13	5	3	1		4	9	4	3	1	1	
11–20	73	45	12	14	2		14	31	12	11	8		
21–30	37	19	10	8			4	15	1	6	3	5	
31–40	42	24	9	7	2		6	18	5	7	5	1	
41–50	18	7	7	4			3	4		1	2		1
51–60	6	3	2	1			1	2		2			
61–70	3	1	0	2				1			1		
71–75	1		1										
0–75	206	114	48	39	5		34	80	22	30	20	7	1

* Note cases lost between first and second tests.

minimize a possible error on the basis of anergy induced by extensive, progressive lesions. This selection also militated to some degree against the most favorable showing by radiological methods which, of course, miss few, if any, advanced pulmonary lesions. It may be admitted, of course, that ultimate diagnosis requires more than X-ray determination of infiltration. Cases with doubtful calcifications were considered as noncalcific.

Tuberculin skin tests were then made by the intracutaneous technique, 0.1 mg. of commercial OT being employed as the first dose, followed in one week by 1.0 mg. if the reaction had been negative or equivocal. Reactions were graded by the standard criteria, considering the total wheal and central oedema (17).

Physical examinations were also given each patient, but the results are not included in the present analysis, inasmuch as it is generally conceded that, as routinely accumulated, such data are inferior to those of the other two methods, and may best be utilized for the further careful study of those individuals already diagnosed, that is, in determining relative

TABLE 2

Distribution of positive and negative reactions to PPD and OT in 317 consecutive cases subgrouped according to presence (+) or absence (−) of tuberculous foci at pulmonary hilum (H) and in parenchyma (P)

CALCIFICATION	TUBERCULIN REACTION	OT 0.1 MG.	PPD .000,02 MG.	OT 1.0 MG.	PPD .005 MG.
H+ P−	+	24	14	7	8
	++	14	8	6	3
	+++	7	3	2	2
	++++	0	0	0	0
	−	28	48	10	12
H− P+	+	3	2	1	3
	++	1	0	0	0
	+++	1	0	1	0
	++++	0	0	0	0
	−	5	8	2	1
H+ P+	+	34	33	19	15
	++	44	16	9	4
	+++	21	21	4	2
	++++	2	2	0	0
	−	84	113	28	39
H− P−	+	14	6	6	10
	++	7	5	1	2
	+++	3	2	0	0
	++++	0	0	0	0
	−	25	36	21	16
		175 (55%)+	112 (35%)+	56 (48%)+	49 (42%)+
		142 (45%)−	205 (65%)−	61 (52%)−	68 (58%)−

aeration, bronchial obstruction, etc. Data pertaining to this group of persons are presented in table 1.

The second group of individuals comprised 317 consecutive clinic patients with or without X-ray evidence of lesions significant of tuberculous infection and excluding only advanced cases of disease for reasons noted before. Ages were not noted among these patients, but subgroup-

ing is possible on the basis of the absence or location in the chest of the significant X-ray lesion, usually calcification.

These patients were then tested with Mantoux technique, introducing simultaneously into the skin of one forearm .000,02 mg. of Purified Protein Derivative and into the other .1 mg. of OT. In cases where both tuberculin tests were negative, or one was negative and the other equivocal, or both were indeterminate, second tests were done in one week, employing .005 mg. of PPD and 1.0 mg. of OT.

As in the first group physical examinations were done, but not included in the present analysis. Data pertaining to this second group of cases

TABLE 3

Comparison of degree of reaction to PPD and OT in 317 consecutive clinic cases unselected except for elimination of advanced tuberculous infiltrations. The lower line of figures notes cases reacting positively to one tuberculin but negatively to the other

OT 0.1 MG. > PPD .000,02 MG.	OT 1.0 MG. > PPD .005 MG.	OT 0.1 MG. = PPD .000,02 MG.	OT 1.0 MG. = PPD .005 MG.	OT 0.1 MG. < PPD .000,02 MG.	OT 1.0 MG. < PPD .005 MG.
110	35	178	71	29	19
OT+ PPD−	OT+ PPD−			OT− PPD+	OT− PPD+
76	21			12	13

TABLE 4

Correspondence of detection (+) and nondetection (−) of tuberculous foci among 317 persons by tuberculin testing with both PPD and OT, and by fluoroscopy

TUBERCULIN + FLUOROSCOPY +	TUBERCULIN + FLUOROSCOPY −	TUBERCULIN − FLUOROSCOPY +	TUBERCULIN − FLUOROSCOPY −
210	31	59	16

are presented in tables 2, 3 and 4 and are combined with those of the first group in table 5.

In the radiological evaluation of both groups the fluoroscope was employed with corroborative single films wherever interpretation appeared questionable. Fluoroscopic findings have been shown in previous studies by the author (10) and others (5, 6, 7, 14) to be dependable when compared with films. In this connection it may be added that in the determination and localization of calcifications, particularly at the hilum, fluoroscopy is, in the author's opinion, a method superior to the flat or single X-ray film. In such films there frequently occur well defined,

smooth-bordered densities in the hilum zone of the lungs which may be difficult to interpret as between small calcifications and long-axis views of trunk markings or of vessels filled with blood. Such difficulty rarely arises or is usually easily solved by fluoroscopy by slight rotation of the patient, or movement of the tube, or observation in various phases of respiration, especially in forced expiration which serves to empty large central vascular channels. The ease of examination of the retrocardiac area is also a decided advantage of fluoroscopy as pointed out elsewhere (10). On the whole, in experienced hands and with adequate equipment fluoroscopy appears to be a thoroughly dependable method of radiological chest examination. Possibly its gravest fault is the absence of permanent, objective records.

The commonest X-ray evidence of past tuberculous infection is calcification as seen in the Ghon tubercle or the Ranke complex (4). In the

TABLE 5

Distribution of degree of reaction in 474 first tests of OT 0.1 mg. and in 169 second tests of OT 1.0 mg.

REACTION	OT 0.1 MG.	OT 1.0 MG.
− −	231	62
+	109	57
++	98	35
+++	34	14
++++	2	1

present study it has been assumed, as is generally done, following the work of Opie that all such formations are of tuberculous origin, though a minor objection to this conclusion may be raised in view of the occasional occurrence of calcification in the healing of other inflammatory and destructive pleural and pulmonary lesions (3). The common assumption that calcific lesions are always significant of a first-infection type of tuberculosis would also appear questionable in view of the similar appearances of calcifications shown by serial observation to result from reinfection types of disease. Of course, not every tuberculous infiltration, either primary or secondary, leaves calcification as evidence of its previous existence, many completely disappearing or showing only fibrous transformation. In addition to this group a certain small percentage of cases will be undetected by roentgenological studies because the lesions are extrapulmonary.

DISCUSSION

Data pertaining to the first group of patients are analyzed in relation to age groups in table 1. In those subgroups containing a sufficient number of individuals to permit statistical evaluation it is interesting to note that the percentages of positive and negative reactions to the initial tests were highly constant despite age. This is contrary to the common opinion that increased time after tuberculous activity is associated with reduced sensitivity to tuberculin. A similar constancy is noted in the results of the second tests. These observations suggest that, with increasing antigenic potency attained by variation of type or increased amount of tuberculin injected, an approach should be made to a 100 per cent standard represented by the entirety of a group of infected or formerly infected persons. In the present analysis, as already pointed out, the X-ray demonstration of a significant lesion or calcification is taken as indicative of such infection, and with increasing dosage or potency one might therefore expect positive tuberculin results in all of the present selected group. This attainment is, of course, limited by the number of infected persons whose reactivity has dropped or remained below a threshold level to a reasonable dose of tuberculin. Such unresponsive cases are often assumed to be inactive from the standpoint of tuberculous disease, although of the 317 patients of group 2, 7 were found showing negative tuberculin reactions despite minimal exudative infiltration proved tuberculous by subsequent observation. Furthermore while the assumption of tuberculous inactivity in tuberculin-negative reactors may pertain more or less accurately to current clinical disease, it does not necessarily extend to future pathogenicity. The recent work of Feldman and Baggenstoss (16) in demonstrating the sterility of calcified encapsulated tuberculous lesions is important in this regard. It would appear, however, to be quite as important from the individual and clinical view point, as well as from the epidemiological approach, to know not only the cases responsive to certain arbitrary tuberculin dosages, but also those with nonreactive infection or disease detected by other objective methods, in this instance radioscopy. Claims made for tuberculin testing have usually referred to its value in the detection of infection as distinct from disease. Its demonstration of activity of disease has appeared less dependable. Similar claims can, of course, be made for radiographic methods except in cases with extrapulmonary or noncicatrizing infection, but with the added advantage of a keener index of clinical activity of the lesions found. It would appear to be important

in survey work, whether for the detection of clinical disease or of infection only, that that method of examination be used which will most inclusively present both infection and disease for further study. A greater number of inactive infections brought to careful scrutiny would not be objectionable especially in view of other clinically active cases also detected which might have remained unrecognized by another method of examination.

Considering the first tests of all patients of group 1, it is seen that of these individuals with definitely calcific foci 55 per cent failed to respond, 25 per cent showed a mild reaction, 19 per cent a moderate reaction and 2.4 per cent a severe reaction. A similar gradation of results pertained to all age subgroups.

Of the second tests 27 per cent remained negative, while 37 per cent showed mild, 25 per cent moderate and 10 per cent intensely positive reactions. Twenty-two cases remained negative to both tuberculin tests; these comprise 25 per cent of the cases submitted to second tests and 11 per cent of the original 206 patients examined. This group constituted a low percentage of nondetection. With it, however, should be considered a second source of error, not usually included in the statistics of such studies, but apparently occurring in the experience of others (2) as well as of ourselves. Thus of the 114 patients nonreactive to the first tests, only 80 were returned for reëxamination by the second test, 34 cases thus being lost, or 16 per cent of the original group of patients. This loss from an entirely voluntary group was in spite of an excellent follow-up system, and was in large measure due to the objections of patient or parent to a repetition of the test. While obviously these cases cannot be charged against the scientific accuracy of tuberculin testing, they do constitute an important source of error in its practical application. Thus if one combines with the cases negative to both tuberculin tests those lost between tests, there is a resultant error of 27 per cent of the original group of patients. Such a figure is of considerable practical importance in the examination of large groups.

The second group of patients by reason of the nature of the material and tests permits a wider analysis than the first, and the testing with both tuberculins permits contrast of their results pertaining to this group. That such simultaneous application of tests is without notable effect on their results has been shown by McCarter, *et al.* (2).

In table 2 all cases of this group are arranged as to the presence or absence of pulmonary calcification and its location, if present, in terms of

hilar or peripheral position. Thus "H-positive P-negative" indicates that calcification was detected at the hilum, but that no parenchymal lesion was discovered. Other subgroups are then easily understood. These groups are then further subdivided according to the degree of reaction to tuberculin as above noted.

It is seen that in all groups and to both types of tuberculin the greater percentage of positive tests were of the mild type with gradation to the more severe ones. It is further interesting to note again the constancy of positive to negative reactions in all groups, though at different levels for the two types of tuberculin. Thus in the first tests 56 per cent of cases reacted positively to .1 mg. of OT as against 35 per cent with .000,02 mg. of PPD. Of the second tests 48 per cent were positive with 1.0 mg. of OT as against 42 per cent with .005 mg. of PPD.

Such observations are susceptible to two interpretations. Thus the test resulting in the higher percentage of positive reactions may be the more accurate inasmuch as it more closely approaches a theoretical maximum. On the other hand, such a test may be giving a greater number of false positive reactions. Under the conditions of the present experiment, at least, the particular preparations of OT used appeared more capable than was the PPD of eliciting a response expected on the basis of X-ray findings. According to the above interpretations this would be equivalent to its greater accuracy. The author is fully aware, however, of the possible inconstancy of such potency as a result of varying methods of preparation of OT. Several brands of OT have, however, all appeared more reactive than the presumably equivalent doses of PPD.

A second observation of interest is the fact that the percentage of positive and negative reactors in groups of statistical size appear to be independent of the location of calcification within the lung or even its complete absence from the chest. It is possible, of course, that extrapulmonary foci may serve in part to maintain responsiveness to tuberculin, but it remains notable that no significant variation of sensitivity can be discerned.

Such observations suggest that the conditions actually being detected by radiology on the one hand and tuberculin tests on the other may be largely independent. Thus radiology is employed in the detection in the lungs of inflammatory products of exudative, fibrous or calcific nature without reference to allergy or anergy. Tuberculin testing, on the other hand, is presumed to detect conditions of sensitivity to tuberculin. It

would appear that, in view of the significance of both these types of information, it would be impracticable from the standpoint of clinical or epidemiological considerations to use either method alone as a screen.

It will be noted that the percentage of reactions positive to 0.1 mg. of OT in all cases of group 2 is 10 per cent higher than that in group 1 above, while the percentage of reactions positive to 1.0 mg. of OT is 25 per cent less in group 2 than in group 1. The causes of such inconsistency are not apparent, but may be found in the variables surrounding tuberculin testing, especially with OT.

A rearrangement of the data of the second group as in table 4 shows agreement between fluoroscopy and tuberculin testing to the extent of 66 per cent in terms of positive reactions, and 5 per cent in negative reactions. This comprises a total agreement of 71 per cent. Cases reactive to tuberculin, but without fluoroscopic evidence of infection, constituted 9.7 per cent, while cases showing fluoroscopically significant lesions, but negative to tuberculin testing, comprised 18.6 per cent. This latter figure is more than three times greater than a comparable one found by McPhedran and Opie, quoted by Long (8), and included seven instances of exudative infiltration with negative tuberculin reactions. It is thus apparent that approximately a 9 per cent greater error would be incurred in this group by examination with tuberculin alone than would result from fluoroscopy alone. It should furthermore be recalled that the tuberculin tests referred to here are double ones, including in each instance both OT and PPD, a test being considered positive if only one responded. As will be shown later, there is further disagreement between results to these tuberculins themselves, so that in actual practice the percentage of error in tuberculin testing alone would exceed that in fluoroscopy alone by something more than the 9 per cent of this experiment. It is, of course, obvious that the accuracy of the combined use of tuberculin and fluoroscopy exceeds that of either alone.

If the data of group 1 be combined with those of group 2 pertaining to the reactions to OT without reference to the PPD, it is seen that of a total of 474 cases examined, all of which had been shown to have radioscopic evidence of tuberculous infection, 49 per cent gave reactions negative to 0.1 mg. of OT while 37 per cent of 169 second tests gave reactions negative to 1.0 mg. of OT. This latter group, negative to both tests, constitutes 13 per cent of the original 474 cases examined. If a proportional number of the 28 cases lost in the first experiment between the first and second tests and of the 34 cases so lost in the second experi-

ment were considered as positive or negative, the total percentage of error would, of course, be still higher. As pointed out above, however, all such lost patients should be considered an inherent error of the method. The 62 cases thus lost in the combined groups comprise an additional 15 per cent error, raising the total actual deficiency of tuberculin testing in terms of positive fluoroscopic diagnosis to 26 per cent, under the conditions of the present experiment. That is, tuberculin testing as ordinarily applied with OT has failed in this experiment to detect 26 per cent of the cases of tuberculous infection recognized by fluoroscopy while in the available group, the opposite is the case in only 9.7 per cent. It is obvious that such an error must be of considerable significance, whether in detection of active clinical disease or in study of the epidemiology of the infection.

The failure of tuberculin testing in such a percentage of cases would appear to constitute a serious objection to such large group investigation for tuberculosis as suggested by Stewart (13). The not infrequent observation of cases with pulmonary calcification and with tuberculin tests negative on one examination, but positive later without radiological change, would seem to be a further drawback. It is to be expected of such a biological reaction as the tuberculin test that it would show variation in sensitivity which at times might become so low as to be subthreshold to a given dose of tuberculin which might later give the response expected in the first test. It would not appear necessary to explain every such occurrence on the basis of sensitization by tuberculin itself, or even by the augmentation of a preëxisting subliminal sensitivity by the tuberculin.

Turning again to the data of group 2 in table 3, relative to the comparative effectiveness of OT and of PPD it is apparent that at least the brands of OT used were more sensitive than the PPD. Thus among the first tests by both tuberculins, 56 per cent of cases showed equally positive or negative reactions. In 35 per cent of cases the OT was more decisive than the PPD while the opposite was true in only 9 per cent. Of the second tests, 57 per cent of results were equally positive or negative, while 28 per cent showed reactions more decisive to OT than to PPD with 15 per cent the opposite. If one considers from among such cases of disagreement those in which one tuberculin gave a positive reaction and the other a negative one, it is seen that 24 per cent of the total number tested would have been overlooked in the first test if only PPD had been used. The error in case only OT had been used would have

been 4 per cent. Among the second tests the percentages would have been 17 per cent against 10 per cent. It is therefore clear that a considerably greater number of cases were detected by OT than by PPD under the conditions of this experiment. As pointed out above this may be correlated with greater specific sensitivity rather than with excessive false positive results. The difficulty of interpretation of such data has been noted by others (15), and the above findings have not been universal (12). It may further be noted that the two cases of necrotic ulceration seen in the combined series were both with PPD.

CONCLUSIONS

1. Two experiments are recorded, contrasting the results of tuberculin testing and fluoroscopy as methods of mass survey for detection of tuberculous infection.

2. It is apparent that, while for neither method can complete accuracy be claimed in terms of the other, error would be less in these experiments with fluoroscopy alone than with tuberculin testing alone.

3. It is apparent that the "tuberculin screen" so widely used in survey work may be subject to an error approximating 25 per cent in its epidemiological application.

4. A routine of examination, consisting in simultaneous tuberculin testing and fluoroscopy, is subject to less error than is incurred by the use of either method of examination as a "screen" for the other. The combined use of both methods would appear desirable in clinical as well as epidemiological surveys in view of this greater general accuracy, as well as in view of 7 cases showing exudative lesions, roentgenologically, but negative tuberculin reactions.

5. Under the conditions of the present experiment, OT was appreciably more sensitive than PPD.

6. Sensitivity to tuberculin does not appear dependent upon location or even absence of pulmonary calcification, thus suggesting a divergent significance of the two types of findings, and again the desirability of routine use of both methods of examination.

7. By the use of fluoroscopy the cost of reliable radiological examination is not prohibitive to its general application.

REFERENCES

(1) Long, E. R.: Modern measures in mass control of tuberculosis, Puerto Rico J. Pub. Health & Trop. Med., 1935, *10*, 417.

(2) McCarter, J. H., Gedd, R. H., Stiehm, R. H.: A comparison of intracutaneous reac-

tions in man to the Purified Protein Derivative of several species of acid fast bacteria, Am. J. M. Sc., 1938, *194*, 479.
(3) Norris, G. W., and Landis, P.: Diseases of the chest, W. B. Saunders Co., Philadelphia, 1929.
(4) Fishberg, M.: Pulmonary tuberculosis, Lea and Febiger, Philadelphia, 1932.
(5) Reid, A. C.: Tuberculosis case-finding, Am. J. M. Sc., 1934, *188*, 178.
(6) Hetherington, H. W., and Flahiff, E. W.: Fluoroscopy in tuberculosis case-finding, Am. Rev. Tuberc., 1933, *27*, 71.
(7) Fellows, H. H.: Value of fluoroscope in case-finding, Am. J. Pub. Health, 1935, *25*, 109.
(8) Long, E. R., and Seibert, S. B.: Further studies on Purified Protein Derivative of tuberculin, Am. Rev. Tuberc., 1937, *35*, 281.
(9) Lord, F. T.: The differential diagnosis of pulmonary tuberculosis, M. Clin. North America, 1938, *22*, 701.
(10) Knies, P. T.: Mass surveys for tuberculosis, Christian Birthday Volume, Waverly Press, Baltimore, 1936, pp. 484–490.
(11) Deegan, J. K.: Present status and technique of tuberculin testing, New York State J. Med., 1931, *36*, 1883.
(12) Plunkett, R. E., and Siegal, W.: A comparative study of Old Tuberculin and Purified Protein Derivative, Am. Rev. Tuberc., 1937, *35*, 296.
(13) Stewart, C. A.: Periodic accrediting of households, Am. J. Dis. Child., 1937, *54*, 699.
(14) Bloch, R. G., Francis, B. F., Eisele, C. W., and Mason, E. W.: Roentgenological group examinations for tuberculosis, Am. Rev. Tuberc., 1938, *37*, 174.
(15) Bloch, R. G., Larson, A., and DeGuevara, A.: A clinical experience with synthetic medium tuberculin, Tr. Natl. Tuberc. A., 1929, p. 195.
(16) Feldman, W. H., and Baggenstoss, A. H.: Am. J. Path., 1938, *14*, 473.
(17) Diagnostic Aids, National Tuberculosis Assn., 1922.

TUBERCULOSIS SURVEY OF AN ENTIRE COMMUNITY[1]

ROBERTS DAVIES AND C. A. SCHERER

During recent years several studies have emphasized the importance of tuberculosis surveys of the whole population of a community. The State Department of Health of Tennessee has reported such a survey of the Negro population of Kingsport, and Wells and Smith have reported a similar study in Kingston, Jamaica. In Detroit the public health nurses are instructed to urge the entire population of certain areas with a high tuberculosis mortality to be examined.

In addition to the collection of scientific data, such surveys are of immediate practical importance. They permit the discovery and isolation of all the foci of tuberculous infection in a community. They uncover early cases of disease that may be treated while their prognosis is still good. They identify those cases of apparently inactive disease that should be repeatedly checked for evidence of activity. It is extremely doubtful that any other method will fulfill the same functions to the same degree.

This paper is a report of a study of the whole population of a township in St. Louis County, Minnesota, with the emphasis on finding new cases of active tuberculosis. The population of the community is 367. With the exception of a few families, they are all of Finnish birth or descent. Sixty-five per cent of the population is foreign born. The people earn a living chiefly from their farms. The soil is poor and the economic status of the community is low.

Our procedure was to visit each house in the community, explain the purpose of the survey, take a brief history of the family, and give Mantoux tests to everybody. PPD was used for all skin tests. The usual first-strength dose of .000,02 mg. was used for the first test, and all who did not react within forty-eight hours were retested with one-half the usual second strength dose, or .002,5 mg. We used the weaker solution because we were afraid that a few severe reactions, such as have been reported frequently from the full second-strength dose, might lose us

[1] From the Nopeming Sanatorium and the St. Louis County Health Department, Nopeming, Minnesota.

the full coöperation of the community. All positive reactors were taken to the Sanatorium for X-ray films. Single chest plates were taken at 72 inches with 0.1 second exposure, using 100 milliamperes and from 66 to 90 kilovolts, depending upon the thickness of the chest. All films were interpreted by Dr. G. A. Hedberg of the Sanatorium staff.

Of the 367 people in the community 66 were not adequately examined. Nine refused to be tested, 29 could not be contacted, 10 with positive Mantoux tests were not X-rayed and 18 with negative first-strength Mantoux tests were not examined further. The distribution of positive Mantoux tests and the various X-ray findings are not essentially different from those of other surveys. Sixty-two per cent of the males and 57 per cent of the females examined had positive tuberculin reactions. One-third of these positive cases reacted to the second test only; 123 of 218 X-ray films taken were negative for tuberculosis. There were 56 cases showing only healed primary tuberculosis and no cases of active primary tuberculosis. Thirty-two cases of healed tuberculosis of the adult or reinfection type were found, of which 25 were minimal, 5 moderately advanced and 2 far advanced. Half of these inactive cases were negative to the first Mantoux test. Of course, all the cases in young people and any others classified as inactive in which there was any suspicion of activity were filed for future check-up.

The important result of the survey was that 6 previously unknown cases of active tuberculosis were found; 2 of these had positive sputum. One of the cases was far advanced and the other 5 were moderately advanced. All of them were immediately hospitalized and treated. At the present time, less than a year after the completion of the survey, 5 of these 6 cases have returned home and are classified as arrested. The one remaining case will soon be ready for discharge. These 6 cases were diagnosed early (with the exception of the single far advanced case) and removed from the community. Four of them were hospitalized before they became a menace to others. They have been treated satisfactorily with a minimum expenditure of time and money and have been returned to their homes in good health.

The cost of this survey, including salaries, was approximately $1000.00. Assuming that the average early case requires one year less treatment than the average far advanced case, and that the cost of treatment is $1000.00 a year, by finding 5 early cases we saved the county $5000.00. This is without considering the economic value of isolating these cases and preventing further infection of the community.

Since, on the basis of previous sanatorium admissions, we expected to find an unusual amount of disease in the area we studied, one might object that in only a few communities would there be enough tuberculosis to make the same method practicable. We have therefore tried to compare our results with those of other surveys of similar communities, that is, rural communities with predominantly white population. Such comparison is difficult because we can find no other survey of a similar community which has attempted to examine the whole population and the methods of sampling are not outlined in the published reports. Also, most extensive surveys have not included X-ray films and most other workers have used Old Tuberculin instead of PPD. We do not

TABLE 1

Percentages of positive Mantoux tests in various surveys (all percentages corrected to age distribution of "normal" population)

INVESTIGATOR	POPULATION STUDIED	PERCENTAGE POSITIVE
Korns, Sydenstricker, Downes	Part of white population of Cattauragus County, New York	40.1
Aronson	Part of population of rural communities in Michigan	49.4
Aronson	Part of white population of rural communities in the South	64.7
Davies, Scherer	Total population of rural township in Minnesota	63.9*
Hilleboe	Admissions to Minnesota State Institutions excepting the State Tuberculosis Sanatorium and the Orthopedic Hospital. Tested with .1 mg. OT only	Male 49.4 Female 41.4
Davies, Scherer	Total population of rural township in Minnesota. First Mantoux only	Male 52.5 Female 37.5

* All persons X-rayed without Mantoux test considered as positive.

know accurately how our second-strength test of one-half the usual second dose of PPD compares with their tests. Nevertheless, the comparisons shown in table 1 may be considered suggestive and would seem to indicate that a survey of the total population might profitably be used in other communities. Of course, in an area as comparatively free of tuberculosis as Cattaraugus County, New York, where only one active case was found in over 800 X-rayed, such a survey would not be practical.

It is interesting that only 3 of the 6 active cases found in this survey gave a history of contact with a previously diagnosed case. The other 3 would have been missed by any examination of contacts of sanatorium

admissions, no matter how thoroughly it was done. Also, none of the 5 early cases had any symptoms whatever and would not have reported to a physician until their disease was further advanced.

Everyone feels that case-finding efforts are necessary to remove foci of tuberculosis from a community and to get early cases under treatment while their prognosis is still good. Examination of contacts is probably the most efficient case-finding method since it will presumably give the greatest results for each dollar spent. However, in some areas with a high incidence of tuberculosis a more thorough method seems necessary, and for such communities a Mantoux survey of the whole population with X-ray films of the positive reactors may perhaps be a practical and valuable procedure. We should like to see this method tested in other communities with a high incidence of tuberculosis.

CONCLUSIONS

1. By a Mantoux and X-ray survey which included 301 out of 367 residents of a township, 6 new cases of active tuberculosis were found.
2. The cost of the survey was slight compared with the economic value of the results.
3. The value of the method should be further tested in other communities where the incidence of tuberculosis is high.

We wish to thank the following members of the staff of Nopeming Sanatorium and the St. Louis County Health Department for their coöperation in this survey: Dr. A. T. Laird, Dr. G. A. Hedberg, Dr. E. H. Stahly, Dr. P. C. Welton, Dr. Karl Pfuetze, Mr. Charles Robb, Miss Elizabeth Muckala, Miss Leah Keable, Miss Elma Huttula, Miss Alice Larson, Mr. Charles Haver, Mr. Fred Provencial, Miss Beade Haugerude, Miss Edith Unkenholz, Miss Edith Seglem, Miss Margaret Lundgren, Mrs. Irene Joyce, Mrs. Harold Morkved, Mrs. Mayme Thompson, Miss Berenice LaLiberte and Miss Margot Devich.

BIBLIOGRAPHY

(1) Aronson, J. D.: Further studies of the incidence of tuberculous infection in some rural communities of the South, Am. Rev. Tuberc., 1933, *28*, 617.
(2) Aronson, J. D.: Incidence of tuberculous infection in some rural communities in Michigan, Am. J. Hyg., 1935, *21*, 543.
(3) Douglas, B. H., and Vaughan, H. F.: A new administrative technique in tuberculosis case-finding, Am. Rev. Tuberc., 1937, *36*, 325.
(4) Hilleboe, H. E.: Annual Report Minnesota Tuberculosis Sanatoria under the Supervision of the State Board of Control for 1936.
(5) Korns, J. H.: Tuberculosis in a rural population, The Milbank Memorial Fund Quart. Bull., January, 1934.
(6) Sydenstricker, E., and Downes, J.: The prevalence of tuberculous infection in a rural community in New York State, Ibid., July, 1933.
(7) Wells, C. W., and Smith, H. H.: The epidemiology of tuberculosis in Kingston, Jamaica, Am. Rev. Tuberc., 1936, *34*, 43.

THE EFFECTS OF ULTRAVIOLET RADIATION ON TUBERCLE BACILLI[1]

KENNETH C. SMITHBURN AND GEORGE I. LAVIN

Among workers studying tuberculosis the interest in ultraviolet radiation has centered chiefly on its clinical application. However, it was early recognized that the sun's rays have lethal effects on tubercle bacilli, and subsequently shown that this action was chiefly due to rays in the ultraviolet region. A review of the earlier studies on the clinical use of ultraviolet radiations, and on the effects of these radiations on tubercle bacilli, was published in 1921 by Mayer (1). In 1924 Mayer and Dworski (2) employed rather weak but not well standardized suspensions of tubercle bacilli and found that the organisms were killed by as little as three minutes' exposure at a distance of 5 inches, by the radiation emitted from a quartz mercury vapor lamp. Howze (3) found that tubercle bacilli were killed in five minutes by the radiation of a mercury vapor lamp, but he did not standardize the suspensions and his experiments cannot be regarded as quantitative. Eidinow (4) observed that saline suspensions containing 1 mg. of tubercle bacilli per cc. were rendered nonvirulent by ten or fifteen minutes' exposure to the mercury vapor lamp and believed the rays shorter than 3,300 Å to be the most effective. A year later Mayer and Dworski (5) reported that suspensions containing 2,750,000 tubercle bacilli per cc., exposed at a distance of 2.5 cm. from the window of the lamp, were reduced in pathogenicity in two or three minutes and were made nonvirulent by four minutes' exposure.

Our interest in this subject was stimulated by the work of Stanley (6), Hodes, Lavin and Webster (7), and Kidd (8). Stanley (6) showed that tobacco-mosaic virus protein could be rendered avirulent by ultraviolet radiation, while the immunological activity was retained. Kidd (8) likewise found that the infectivity of the Shope papilloma virus could be abolished by means of ultraviolet radiation without loss of complement binding capacity. Hodes, Lavin and Webster (7) made

[1] From the Laboratories of The Rockefeller Institute for Medical Research, New York City.

different application of the same principles; they found that the infectivity of rabies virus could be eliminated with ultraviolet radiation, and that if the exposure was quantitatively proper the inactivated virus was still able to induce immunity to rabies in mice.

Lavin and Stanley (9) found that the tobacco-mosaic virus protein had its maximum absorption at about 2,650 Å. Burger (10) found that radiation in this range had much greater bactericidal action than did longer wave lengths; he also found that bacteria inactivated with ultraviolet rays made superior vaccines (11). Gates (12) later showed that the maximum absorption of *B. coli* was in the same approximate range and that similar radiation was highly effective in the inactivation of both *Staphylococcus aureus* and its specific bacteriophage (13). Furthermore Spiegel-Adolf and Seibert (14, 15) observed that various tuberculin preparations had absorption maxima at 2,650 Å. A lamp was commercially available which had a maximum energy output in this approximate region. It was, therefore, decided to use this lamp to study the effect of its radiation on the immunizing potency of tubercle bacilli. Simultaneously, studies were made of the effects of the radiation on the viability and virulence of mycobacteria.

MATERIALS AND METHODS

Ultraviolet radiation: The source of radiation employed was a mercury vapor resonance lamp (manufactured by Hanovia Chemical Co., Newark, New Jersey). Approximately 90 per cent of the energy was emitted as radiation of 2,537 Å. Suspensions of tubercle bacilli contained in quartz flasks were exposed to the lamp while being agitated in a mechanical shaker so arranged that the flask was at a constant distance (15 cm.) from the source of radiation. During exposure the quartz flask was sealed with a close fitting gum-rubber cap. The physical set-up is described in detail by Hodes, Lavin and Webster (16).

Intervals of exposure were timed with a stop-watch. At the end of an interval the lamp was screened, the gum-rubber cap was removed from the quartz flask, and the sample of irradiated suspension was removed with a sterile pipette.

Bacteria: Two strains of tubercle bacilli were used in the experiments: a highly virulent line of the well known human strain H37, and a second human type strain designated Lockett, isolated from the cerebrospinal fluid of a patient with tuberculous meningitis (17). The organisms were grown on glycerolated egg-yolk medium adjusted to pH 6.8 (18). Vigor-

ously growing cultures, about three weeks old, were employed. Suspensions were prepared by grinding a weighed quantity of organisms, freshly removed from the tube, in a sterile procelain mortar, with dropwise addition of sterile physiological saline solution in sufficient quantity so that 1 cc. of suspension contained 1 mg. of bacteria. Appropriate decimal dilutions were made from such suspensions to contain the desired quantity of bacteria. Suspensions to be irradiated were at once transferred to the sterile quartz flasks, and suspensions used for inoculation were employed promptly to minimize the sedimentation or agglutination of the organisms.

Animals: Albino guinea pigs, bred in this Institute from stock free of epizootic streptococcal infection, were used in the experiments. Both males and females were used, but animals of different sexes were caged separately. In experiments where groups of animals were to be compared for longevity following inoculation, the groups were arranged either to contain animals of the same sex, or so that the distribution of individuals of different sex was the same in control and test groups. Also, groups to be so compared were comprised of animals of similar individual weights. For the most part the guinea pigs weighed about 400 g. Not more than 4 were caged together.

Inoculations: All inoculations, whether for the purpose of testing the virulence of irradiated organisms, or to test the immunizing potency of vaccine, were made by the intracerebral route. Anaesthesia was induced with ether or by intraperitoneal injection of 0.5 per cent solution of Seconal[2] in saline. The dose of Seconal was 20 mg. per kg. Intracerebral inoculations were done by the method previously described (19).

Vaccinations: Irradiated suspensions containing 1.0 mg. of bacteria per cc. were injected subcutaneously along the right side. Injections were made daily for five days, the daily dose being 0.3 mg. in 0.3 cc. In one experiment test inoculations were done eleven days following the last dose of vaccine. In the other experiment the animals were inoculated fifteen days following the last prophylactic injection.

Tests of viability of irradiated suspensions: These were made by seeding tubes of the glycerolated egg-yolk medium with 0.2 cc. each of suspension. In two experiments tubes were seeded in duplicate; in other experiments 5 tubes were seeded with each irradiated sample.

[2] Sodium Propyl-methyl-carbinyl Allyl Barbiturate, Lilly, generously supplied by Eli Lilly and Company, through the courtesy of Dr. G. F. Kempf, Indianapolis City Hospital.

Control cultures were also made of the nonirradiated suspensions. The tubes were sealed with melted paraffin and incubated at 37°C. They were examined weekly with a hand lens and records were made of the time when growth appeared, of the number of tubes showing growth and of the approximate number of colonies per tube. Final recordings of failure of growth were made only after eight or more weeks' incubation.

Tests of virulence of irradiated suspensions: These were made by inoculating irradiated and control (nonirradiated) suspensions intracerebrally. Two normal animals were used to test each suspension. The dose of organisms was 0.01 mg. or larger. (This dose of virulent organisms introduced intracerebrally usually causes death in about three weeks.) Organisms were considered nonvirulent only when both animals inoculated remained symptom free for six weeks or longer.

Tests of immunization: Two varieties of such tests were made. First, animals which survived the intracerebral injection of a single dose of irradiated organisms (0.01 mg.) and remained well for six or more weeks were reinoculated intracerebrally, together with comparable normal controls, with a small dose of virulent organisms. Second, groups of guinea pigs which had been vaccinated subcutaneously with irradiated organisms, together with normal controls of comparable age, sex and weight, were inoculated intracerebrally with 0.000,01 mg. each of the homologous virulent strain of organisms. In such experiments the results were measured by longevity following virulent inoculation, and the significance of the result was determined by standard methods (20).

EFFECT OF IRRADIATION ON VIABILITY OF TUBERCLE BACILLI

Four separate suspensions of three different densities of human tubercle bacilli, strain H37, were irradiated with the mercury resonance lamp and samples were withdrawn at the intervals shown in table 1. Two to 5 tubes of glycerolated egg-yolk medium were seeded with each sample, sealed and incubated. The final result of the tests is shown in table 1.

It will be noted from the data that, with the least dense suspension (0.05 mg. per cc.), no growth was obtained in any of 60 tubes seeded with irradiated organisms, but the nonirradiated organisms grew massively. The organisms were apparently rendered nonviable by as little as one minute's exposure to the lamp. The suspension of inter-

mediate density (0.1 mg. per cc.) contained a very few viable bacteria after two minutes' exposure to the radiation. One of 2 tubes seeded with this sample showed a single colony; the duplicate tube was negative. However, with a suspension containing 1.0 mg. of organisms per cc., there were still viable organisms after nine minutes' irradiation, while cultures of the ten-minute sample remained negative. This latter confirmed the observation made many years ago by Henri-Cernovodeanu, Henri and Baroni (21). The fact remains unexplained that the three-

TABLE 1

Growth of human tubercle bacilli strain H37 after irradiation for various lengths of time

IRRADIATION	DENSITY OF SUSPENSIONS EXPRESSED AS MG. PER CC.			
	0.05†	0.1	1.0	1.0
minutes				
Control 0	5/5*	2/2	2/2	5/5
0.5		1/2	2/2	
1.0	0/5	0/2		5/5
1.5		0/2		
2.0	0/5	1/2		5/5
2.5			2/2	
3.0	0/5			0/5
4.0	0/5			1/5
5.0	0/5			2/5
6.0	0/5			5/5
7.0	0/5			5/5
8.0	0/5			2/5
9.0	0/5			5/5
10.0	0/5			0/5
12.5	0/5			
15.0	0/5			

* Numerator = number of tubes showing growth. Denominator = number of tubes planted.

† This suspension was cleared of clumps by light centrifugation, then brought to desired density by comparison of turbidity with a standard suspension.

minute sample yielded no growth, and that there were negative tubes from the four- and five-minute samples of this suspension, while all tubes seeded from the six- and seven-minute samples showed growth. It must be remarked, however, that none of the irradiated samples yielded growth equal in quantity to the control nonirradiated samples; and in general it was true that samples irradiated successively longer showed progressively fewer colonies.

Smears of the irradiated bacteria were prepared and stained by the

Cooper method. All the samples shown in table 1 retained their acid-fastness and could not be differentiated in the smears from the control nonirradiated organisms. This observation is contrary to that of Cernovodeanu and Henri (22).

This result indicated that the radiation emitted by the lamp used was capable of quickly rendering tubercle bacilli nonviable when the suspensions were relatively weak, and showed that with more dense suspensions the time required to render the organisms nonviable was considerably prolonged. Furthermore, very short exposure to radiation was effective in reducing the number of viable organisms, but longer exposure was necessary to kill them all.

EFFECT OF IRRADIATION ON VIRULENCE

Three experiments were done to test the virulence of organisms exposed to radiation for varying lengths of time. The nonirradiated and irradiated samples of each suspension were inoculated intracerebrally, each sample into 2 normal albino guinea pigs. Relatively large doses were injected (not less than 0.01 mg.) in order to be able to detect the presence of small numbers of virulent organisms which might survive the irradiation. The H37 strain used in two of these experiments was fully virulent, the Lockett strain slightly less so. From prior experience it was known that 0.01 mg. of fully virulent organisms ordinarily causes death within about three weeks after intracerebral inoculation; and 0.000,001 mg. usually causes death in less than six weeks (19). The experiments were therefore not terminated until six or more weeks after inoculation. Table 2 shows the results of the experiment.

The results shown in table 2 indicated that the Lockett organisms in suspension containing 0.1 mg. per cc. were nonvirulent after two minutes' exposure to the lamp. These animals were observed for sixty-seven days and none showed any ill effects from the inoculations; the control animals inoculated with nonirradiated organisms both succumbed. The middle vertical column in table 2 shows that a similar suspension of the H37 strain was rendered less virulent (the animals living longer than those inoculated with the nonirradiated suspension) by as little as fifteen seconds' exposure to the radiation, and nonvirulent by thirty seconds' exposure. This was the same experiment as that in which a single colony was obtained in 1 of 2 tubes seeded with suspension irradiated two minutes (table 1). The result, therefore, indicated that although viable organisms were present they had either lost their viru-

lence or else were present in such small numbers as to allow survival without evidence of illness for forty-two days after inoculation. The experiment in the last column to the right in table 2 showed that in a heavier suspension of the H37 strain virulent organisms remained after two and one-half minutes' irradiation. This confirmed the result obtained by cultural methods (table 1) and showed that greater exposure to radiation is required for dense suspensions in order to reduce the virulence of the organisms or the number which are viable.

TABLE 2

Virulence of human tubercle bacilli after irradiation, as determined by survival or death following intracerebral inoculation

IRRADIATION	LOCKETT STRAIN 0.01 MG.*	H37 STRAIN 0.01 MG.	H37 STRAIN 0.1 MG.
minutes			
0.25		D 36†	
		D 31	
0.5		S	D 27
			D 44
0.75		S	
1.0		S	
1.25		S	
1.5		S	
1.75		S	
2.0	S	S	
2.5			D 29
			D 36
4.0		S	
6.0	S		
10.0	S		
14	S		
Control	D 30	D 23	
0	D 31	D 24	

* This dose was inoculated in 0.1 cc. saline. The suspension irradiated therefore contained ten times this quantity per 1 cc.

† D indicates death on day shown. S indicates survival of both animals inoculated with a sample.

In summary of the tests of virulence we may say that an unknown number of organisms remained viable and virulent after two and one-half minutes' irradiation of a suspension containing 1.0 mg. of organisms per cc. When the suspension contained only 0.1 mg. of organisms per cc., fifteen seconds' exposure was adequate to appreciably reduce the virulence of the organisms (either by attenuation or by killing off a portion of them) and thirty seconds of exposure to the lamp rendered the organisms nonvirulent.

TESTS OF IMMUNITY AFTER INJECTION OF IRRADIATED ORGANISMS

Each of the animals (table 2) which survived the intracerebral inoculation of 0.01 mg. of either the irradiated Lockett or the irradiated H37 organisms was reinoculated intracerebrally with 0.000,01 mg. of the homologous virulent organisms to ascertain whether the small quantity of organisms made nonvirulent by irradiation had induced measurable immunity. Normal control guinea pigs were inoculated at the same time with the same dose of organisms. All these animals succumbed to tuberculosis, and none of those first inoculated with irradiated organisms were more resistant to the test inoculation than the normal controls. This result indicated that no appreciable immunity is induced by a single intracerebral injection of 0.01 mg. of irradiated tubercle bacilli.

Two additional experiments were done to determine whether enhanced resistance could be induced by subcutaneous injection of larger numbers of irradiated organisms. In both experiments the suspension irradiated contained 1.0 mg. per cc. of the strain H37. In the first experiment two irradiated samples were used as vaccine: one had been exposed to the lamp thirty seconds and the other two and one-half minutes. Both these specimens were found to contain a residuum of viable, virulent organisms (tables 1 and 2). In the second experiment two samples of vaccine were also used. One had been exposed to radiation for five minutes, the other for ten minutes. The five-minute sample was found to contain a few viable organisms (table 1) the virulence of which was not tested. Bacteriological tests indicated that the sample irradiated ten minutes contained no viable organisms. Each of the four irradiated samples of mycobacteria was injected subcutaneously daily for five days in each of a group of 5 or 8 normal guinea pigs. The daily dose for each animal was 0.3 mg. Eleven or fifteen days following the final injections of vaccine, these guinea pigs and comparable groups of non-vaccinated control animals were inoculated intracerebrally with 0.000,01 mg. of the homologous virulent organisms to test their resistance. None of the animals was submitted to other experimental procedure. The criterion of resistance was the length of survival following test inoculation. The results of the experiments are shown in table 3.

The data in table 3 indicate that the animals vaccinated with organisms irradiated for one-half or two and one-half minutes were partially protected against virulent inoculation. Not only was the mean survival significantly prolonged in both these groups, but one animal of the group vaccinated with organisms irradiated two and one-half minutes survived the virulent inoculation and showed no ill effects thereof

seventy-five days later. In the groups vaccinated with organisms irradiated five minutes and ten minutes, the mean survival was not significantly prolonged, but one animal survived in the group vaccinated with organisms irradiated five minutes. This result was considered

TABLE 3

Survival time in days following intracerebral inoculation of 0.000,01 mg. of virulent tubercle bacilli strain H37. Comparison of nonvaccinated controls with animals vaccinated with irradiated H37

VACCINATED WITH H37 IRRADIATION	SURVIVAL IN DAYS		VACCINATED WITH H37 IRRADIATION	SURVIVAL IN DAYS	
	Individual	Mean		Individual	Mean
minutes			*minutes*		
0.5	35 37 41 53 58 60 67 75‡	53.3 ±3.5	5	30 37 39 51 59*	44.0 ±3.4
2.5	47 55 56 58 69 72 75‡ 75*	63.3 ±2.6	10	† 32 43 49 59‡	44.75 ±3.8
Nonvaccinated controls	22 26 28 29 36 39 42 42	33.0 ±1.9	Nonvaccinated controls	28 37 42 45 50	40.4 ±2.6

* Animal in excellent condition. Sacrificed to end experiment.

† Animal succumbed to intercurrent infection.

‡ Animal paralyzed. Sacrificed.

significant because normal, nonvaccinated animals subjected to intracerebral inoculation of 0.000,01 mg. of this line of the strain H37 inevitably succumbed.

From experiments reported earlier in this paper (table 1) we know that the vaccines irradiated respectively one-half, two and one-half and five

minutes contained viable organisms, while the suspension irradiated ten minutes apparently contained none. Thus the three groups of animals which showed demonstrable protection were vaccinated with suspensions which contained viable organisms; and the group which exhibited no protection was vaccinated with a suspension containing no viable organisms. This result would seem to indicate that the radiation rendered the organisms nonviable and inactivated the immunizing capacity at about the same time. However, it is possible that one might irradiate a less dense suspension for a shorter period and render the organisms nonviable while maintaining the immunizing power.

Microscopical surveys of the lesions in the three groups of animals in the left half of table 3 revealed that the preparatory vaccinations influenced the histogenesis of lesions. Pulmonary tubercles were not found microscopically in any of the 8 controls, but there were lesions in the tracheobronchial lymph nodes of all save one. Each control exhibited extensive lesions in the spleen, liver and cervical lymph nodes, and massive, acute tuberculous meningo-encephalitis. The lesions of the spleen and brain showed many tubercle bacilli. In the vaccinated groups, on the other hand, the lesions in brain and meninges were considerably less extensive (sometimes minimal), more of the hard type of tubercle and contained fewer organisms. We have previously described and illustrated similar lesions in animals vaccinated by other methods (23). Lesions in cervical nodes of the vaccinated groups were also less extensive. But lesions in other viscera such as spleen and liver were as extensive as in the controls. Moreover, the vaccinated animals in a few instances exhibited pulmonary lesions, possibly due to the fact that they survived longer.

Thus the vaccinations with irradiated suspensions containing viable bacteria afforded partial protection, as expressed by significantly greater survival and by complete protection of a small number of animals; and vaccination also exerted an inhibitory influence on the evolution of the local cerebral and meningeal lesions, but exerted no favorable influence on the development of metastatic lesions. (It is possible that a part of the visceral lesions in the vaccinated animals may have been caused by the vaccinations.) An irradiated suspension which contained no viable organisms gave no evidence of protection against virulent inoculation.

DISCUSSION

The significant points brought out by this investigation are: first, that ultraviolet radiation may be so applied to tubercle bacilli that they are

rendered nonvirulent without being made nonviable; and second, that irradiated viable tubercle bacilli may induce demonstrable immunity in experimental animals.

Regarding the first point we believe that the reduction in virulence is probably an effect on the individual bacterial cell which precedes the lethal effect occurring with prolonged exposure to radiation. The only other apparent explanation of the effect would be to assume that the reduction in virulence is due to early death, during irradiation, of a large proportion of the bacterial population; but that the survivors are virulent. The results show that early death of a portion of the bacteria does occur; but the methods used to study virulence are so sensitive, and the dose of organisms used to test the virulence of irradiated suspensions was so large, that death would certainly have occurred had virulent organisms been present in the inocula. However, suspensions which failed to cause death when inoculated intracerebrally still contained organisms which grew in culture.

This latter point may have a bearing on the view held by some workers that bacteriological methods are superior to animal inoculations for detecting tubercle bacilli. It is possible that their opinions are based on obtaining in culture attenuated organisms which are incapable of inducing disease in animals.

Regarding immunization with viable irradiated organisms it must be emphasized that this procedure is not recommended for practical purposes as it would undoubtedly be associated with unwarranted hazards. In our experiments, organisms killed by irradiation did not induce demonstrable immunity. However, we used in these experiments dense suspensions which required long exposure to the lamp (ten minutes) to render the organisms nonviable. The heavy suspensions were used because we desired to have a given quantity of organisms in the irradiated suspension to be used as vaccine. This result could be accomplished by other methods, and the possibility remains that a weak suspension might be used in which very short exposure to radiation would cause death of the bacteria, conceivably without denaturing or rendering ineffective the immunizing antigen.

SUMMARY

The effect of approximately monochromatic ultraviolet radiation (2,537 Å) upon saline suspensions of human tubercle bacilli has been studied. The following effects on the viability, staining properties, virulence and immunizing power were observed.

Heavy suspensions of tubercle bacilli (1 mg. per cc.) require relatively long periods of irradiation (ten minutes or more) to be rendered nonviable. Weaker suspensions are killed in shorter time.

Organisms killed by ultraviolet radiation retain the property of acid-fastness.

Heavy suspensions of tubercle bacilli are rendered avirulent only after relatively long exposure to ultraviolet radiation; but weak suspensions are quickly reduced in virulence. Reduction in virulence can be demonstrated after less irradiation than is required to kill the organisms, and organisms may be made avirulent without being killed.

Irradiated viable organisms possessed the capacity of inducing demonstrable immunity. Organisms killed by the radiation did not induce measurable immunity.

REFERENCES

(1) MAYER, E.: Am. Rev. Tuberc., 1921, *5*, 75.
(2) MAYER, E., AND DWORSKI, M.: Ibid., 1924, *10*, 166.
(3) HOWZE, H. H.: Ibid., 1926, *13*, 470.
(4) EIDINOW, A.: Brit. M. J., 1927, *2*, 160.
(5) MAYER, E., AND DWORSKI, M.: Am. Rev. Tuberc., 1932, *26*, 105.
(6) STANLEY, W. M.: Science, 1936, *83*, 626.
(7) HODES, H. L., LAVIN, G. I., AND WEBSTER, L. T.: Ibid., 1937, *86*, 447.
(8) KIDD, J. G.: Proc. Soc. Exper. Biol. & Med., 1938, *37*, 657.
(9) LAVIN, G. I., AND STANLEY, W. M.: J. Biol. Chem., 1937, *118*, 269.
(10) BURGER, G. N.: Bull. Basic Sc. Research, 1928, *2*, 46.
(11) BURGER, G. N.: Ibid., 1928, *2*, 55.
(12) GATES, F. L.: J. Gen. Physiol., 1930, *14*, 31.
(13) GATES, F. L.: J. Exper. Med., 1934, *60*, 179.
(14) SPIEGEL-ADOLF, M., AND SEIBERT, F. B.: Proc. Soc. Exper. Biol. & Med., 1933, *31*, 351.
(15) SPIEGEL-ADOLF, M., AND SEIBERT, F. B.: J. Biol. Chem., 1934, *106*, 373.
(16) HODES, H. L., LAVIN, G. I., AND WEBSTER, L. T.: In press.
(17) SMITHBURN, K. C.: Proc. Soc. Exper. Biol. & Med., 1938, *38*, 574.
(18) SMITHBURN, K. C.: J. Exper. Med., 1936, *63*, 95.
(19) SMITHBURN, K. C.: Ibid., 1936, *64*, 771.
(20) PEARL, R.: Medical biometry and statistics, Philadelphia, W. B. Saunders Co., 1923.
(21) HENRI-CERNOVODEANU, MME., AND MM. HENRI, V., AND BARONI, V.: Compt. rend. Acad. d. sc., 1910, *151*, 724.
(22) CERNOVODEANU, MLLE., AND M. HENRI, V.: Ibid., 1910, *150*, 729.
(23) SMITHBURN, K. C.: Am. Rev. Tuberc., 1939, *39*, 383.

VITAMIN C AND IMMUNITY IN TUBERCULOSIS OF GUINEA PIGS[1]

FRED H. HEISE AND WILLIAM STEENKEN, JR.

An abundance of vitamin C fed to guinea pigs before and after infection with large numbers of virulent tubercle bacilli did not influence the course of the disease. It was thought that, when the infecting dose was smaller, some effect might be noticed. In the previous experiments 300,000 bacilli were given subcutaneously; in the following experiments 10,000 bacilli were given by the same route. In these experiments, too, the effect of vitamin C was studied in vaccinated and nonvaccinated guinea pigs.

One hundred tuberculin-negative albino guinea pigs were divided into four groups of 25; each group contained the same number of males and females. Two groups were vaccinated subcutaneously with a forty-day old resistant variant dissociate of H37 tubercle bacilli. Three doses of 2.5 mg. each were given on alternate days. All 50 of the guinea pigs reacted to 5 per cent OT intracutaneously two weeks later. Twenty-five vaccinated and 25 nonvaccinated pigs were then given daily 22 mg. of partially neutralized crystalline Cebione subcutaneously. At the end of two weeks the 50 pigs were infected subcutaneously with 10,000 tubercle bacilli of H37 *Rv* variant. The vitamin C was continued daily throughout the ten months of the experiment.

Twenty-five vaccinated and 25 nonvaccinated guinea pigs were likewise infected with H37 *Rv* variant but these groups had not received nor were they given any Cebione.

Intercurrent disease caused the death of 18 pigs; 4 in the Cebione control, 2 in the Cebione, 7 in the Cebione-vaccinated and 5 in the vaccinated group. Six pigs died of tuberculosis before the termination of the experiment. All were in the nonvaccinated groups. Two were in the Cebione control and 4 in the Cebione group. At the end of ten months there remained alive in the nonvaccinated groups 19 in the Cebione control and 19 in the Cebione group. In the vaccinated groups 18 remained in the Cebione and 20 in the non-Cebione group.

[1] From Trudeau Research and Clinical Laboratory, Trudeau, New York.

All living guinea pigs were then killed and autopsied. In the nonvaccinated group as in the vaccinated group no major differences could be seen in the amount and character of the tuberculosis between those pigs receiving vitamin C and those not receiving it. There was a marked difference, however, in the development of tuberculosis in the vaccinated as compared to the nonvaccinated pigs. The vaccinated pigs showed marked resistance in that the amount of tuberculosis in the lungs, liver, spleen and lymph nodes was only a fourth or less of that found in the nonvaccinated pigs.

Vitamin C determinations were made on the blood sera of 5 animals from each of the four groups. No marked differences were noted in any group. Variations occurred from 0.88 mg. per cent to 1.66 mg. per cent.

Sixteen animals not receiving Cebione and 15 which did receive it were tested intracutaneously for tuberculin sensitivity with 0.1, 0.5, 1.0 and 2.0 per cent OT. No marked difference in skin sensitivity was noted between the groups.

Rotter's (2) intracutaneous test for vitamin C was tried in the controls and Cebione group. In the Cebione group decolorization did not take place sooner than in the controls.

During the experiment one of the tuberculous control pigs gave birth to three babies. These were left in contact with their mother. The three did not react to OT intracutaneously one month after birth. At the end of three months one developed skin hypersensitivity and later died. H37 *Rv* bacilli were recovered at autopsy.

CONCLUSIONS

Vitamin C given subcutaneously and in abundance

1. Does not influence the course of tuberculosis in guinea pigs infected with 10,000 H37 *Rv* bacilli;
2. Does not influence the vitamin C blood serum content;
3. Does not influence tuberculin sensitivity in tuberculous guinea pigs.

Rotter's test proved of no value in differentiating supervitaminosis C.

REFERENCES

(1) HEISE, F. H., AND MARTIN, G. J.: Supervitaminosis C in tuberculosis, Proc. Soc. Exper. Biol. & Med., 1936, *35*, 337.

(2) ROTTER, H.: Determination of vitamin C in living organism, Nature, 1937, *139*, 717.

PATHOLOGICAL CHANGES IN PULMONARY TUBERCULOSIS IN JAMAICAN NEGROES[1]

C. W. WELLS

Studies of tuberculosis conducted in Jamaica, British West Indies, during the past nine years have included postmortem examinations of patients dying with pulmonary tuberculosis. This report gives the pathological findings in 113 autopsies of Jamaican Negroes, performed as opportunity and permission could be obtained. The majority of the cases were on the register of the Kingston Tuberculosis Dispensary and, with one exception, all of the patients died while inmates of the local Alms House. For those who did not pass through the Tuberculosis Dispensary a clinical history was unobtainable.

The cases included in this study were all Negroes, comprising 58 males and 55 females; the majority were over eleven and under fifty years of age, the average being 28.9 years.

Adult and childhood types of progressive pulmonary tuberculosis may often be differentiated by X-ray, but in many instances such examinations are inconclusive. Autopsy findings, especially when supplemented by X-ray films of the excised lung, usually provide sufficient evidence to catalogue properly the type of disease. In this study the freshly excised lung was routinely X-rayed, in many instances after being inflated. Such examinations often revealed small calcified pulmonary nodules which otherwise might have escaped notice. The criteria employed in this paper for the differentiation of childhood from adult progressive pulmonary tuberculosis have been taken from the Diagnostic Standards published by the National Tuberculosis Association (1) and from Opie (2). Cases have been classified as childhood tuberculosis when caseous tracheobronchial lymph nodes were demonstrated, associated with tuberculous disease in the lung tissue. This condition occurred in 27 instances. In 6 additional cases the tracheobronchial lymph nodes were greatly enlarged and hyperplastic, but

[1] This study was conducted with the support and under the auspices of the International Health Division of The Rockefeller Foundation, in coöperation with the Jamaica Government Medical Department.

grossly no caseation was apparent; these are also included in the group of childhood type of tuberculosis. In 4 other cases definite caseation was found in the tracheobronchial lymph nodes, associated with calcified nodules in the lung substance; these also are classed as childhood tuberculosis, making a total of 37 cases (32.7 per cent) of the entire series.

Adult type pulmonary tuberculosis has been determined in 51 instances by the presence of calcified pulmonary nodules or calcified tracheobronchial lymph nodes, associated with active disease in the lung and an absence of acute involvement in the lymph nodes. In 25 additional cases classed as adult type tuberculosis careful examination, which included routine X-ray of the fresh lung and dissection after fixation, failed to disclose the presence of calcified lesions either in the lymph nodes or lung tissue. In this group, likewise, there was an absence of caseous involvement of the lymph nodes. A total of 76 (67.3 per cent) of the

TABLE 1

Average age, duration of disease and length of residence in Kingston

	CHILDHOOD TYPE PULMONARY TUBERCULOSIS		ADULT TYPE PULMONARY TUBERCULOSIS	
	Number of cases	Average	Number of cases	Average
Average age of all cases	37	21.5 yrs.	76	32.4 yrs.
Average age of individuals over 15 years	31	24.2 yrs.	75	32.7 yrs.
Average duration of illness	28	8.5 mos.	66	15.3 mos.
Average length of residence in Kingston	25	8.6 yrs.	61	15.6 yrs.

cases in this series have been classified as adult progressive pulmonary tuberculosis.

CHILDHOOD TYPE PROGRESSIVE PULMONARY TUBERCULOSIS

Thirty-seven of the 113 cases have been classified as childhood type pulmonary tuberculosis. These persons varied in age from nine months to forty-seven years (table 6), the average being 21.5 years. For those over fifteen years of age the average was 24.2 years. The length of illness was determined in 28 of these cases and averaged 8.5 months. The average length of residence in Kingston for 25 cases was found to be 8.6 years (table 1). The occurrence of hilar lymph node involvement and of pleural effusions and adhesions is presented in tables 2 and 6.

In 3 instances the disease was miliary in character; these were in

children nine months, twenty-two months and six years of age, respectively. In one of these children and in the remaining 34 cases it was possible to determine the site of the primary disease. The primary lesions were distributed in frequency as follows: right lower lobe, 5; right middle lobe, 2; right upper lobe, 12; left lower lobe, 7; left upper lobe, 9. The primary lesion occurred most frequently on the right side

TABLE 2

Occurrence of pleural involvement in 113 autopsies

TYPE	TOTAL NUMBER OF CASES	PERCENTAGE OF TOTAL CASES	PLEURISY WITH EFFUSION					PLEURISY WITH ADHESIONS												
								Unilateral					Complete obliteration							
			Right side	Left side	Bilateral	Total	Per cent	Right side	Left side	Bilateral	Total	Per cent	Right side	Left side	Bilateral	Total	Fibrinous	Fibrous	Both fibrous and fibrinous	Total
Childhood.....	37	32.7	5	3	0	8	21.6	11	12	13	36	97.3	3	8	0	11	11	20	5	36
Adult.....	76	67.3	6	12	1	19	25.0	10	14	51	75	98.7	13	6	6	25	1	71	3	75

TABLE 3

Distribution and character of lung involvement

TYPE	LOCATION OF PRIMARY OR MAJOR PULMONARY LESIONS						CHARACTER OF LUNG INVOLVEMENT			AVERAGE DURATION OF ILLNESS (IN MONTHS) IN RELATION TO CHARACTER OF LUNG INVOLVEMENT			PULMONARY CAVITIES								
													Location					Character of cavity walls			Duration of illness (in months) in relation to walls of cavities		
	Right upper	Right middle	Right lower	Left upper	Left lower	Total	Caseous	Fibrotic	Fibrocaseous	Caseous	Fibrotic	Fibrocaseous	Right lung	Left lung	Bilateral	None	Per cent with cavities	Thick smooth	Thin smooth	Necrotic irregular	Thick	Thin	Necrotic
Childhood..	12	2	5	9	7	35	27	1	7	6.4	?	15.4	8	10	11	8	78.4	9	8	18	12.4	12.3	7.3
Adult....	37	0	1	38	0	76	9	32	35	5.1	18.7	14.7	20	15	39	2	97.4	43	28	10	16.7	17.6	9.3

and 21 times in upper lobes compared to 14 times in the middle or lower lobes (tables 3 and 6).

The distribution of cavities and the character of their walls are shown in table 6.

As might be expected, both from the type of the disease and its short duration, the character of the lung involvement in these cases of childhood tuberculosis was predominantly caseous infiltration, either bron-

chopneumonic or confluent. This type of involvement was found in 34 of the 37 cases in the series. On the other hand, fibrous tissue formation was not entirely absent, but was found in only 8 cases in this series, in conjunction, however, with caseous involvement. In 1 case the reaction in the lung tissue was almost exclusively fibrotic. In 6 of the cases in which fibrous tissue occurred the disease had progressed for more than one year.

The secondary involvement of other organs and tissues is not infrequent in pulmonary tuberculosis; in this group of 37 cases of childhood tuberculosis, lesions were found in other organs in 21 cases, the most

TABLE 4

Distribution of secondary lesions

TYPE	PERICARDIUM		PERITONEUM		MESENTERIC LYMPH NODES		INTESTINES		SPLEEN		LIVER		KIDNEYS		TRACHEA		TOTAL NUMBER CASES
	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	
Childhood....	2	5.4	9	24.3	15	40.5	6	16.2	11	29.7	6	16.2	1	2.7	1	2.7	37
Adult.....	12	15.8	7	9.2	9	11.8	10	13.2	4	5.3	6	7.9	0	—	2	2.6	76

TABLE 5

The proportion of cases of manifest tuberculosis of childhood type according to age at death

AGE AT DEATH (ALL CASES)	TOTAL NUMBER OF CASES	NUMBER WITH CHILDHOOD TYPE	PER CENT WITH CHILDHOOD TYPE
0–14	7	6	86
15–24	39	17	44
25–30	49	13	27
40+	18	1	6

frequent finding being caseation of the mesenteric lymph nodes, tubercle formation in the spleen, and tuberculous peritonitis. Less frequently, secondary lesions were found in the intestines as ulcers, as tubercles in the liver and kidney, tuberculous pericarditis, and ulceration of the trachea (tables 4 and 6).

ADULT TYPE PULMONARY TUBERCULOSIS

Seventy-six cases (67.3 per cent) of the entire series have been diagnosed as adult type pulmonary tuberculosis. Twenty-five of these cases deserve special comment, for the reason that no evidence of calci-

TABLE 6

Childhood type pulmonary tuberculosis

CASE NUMBER	AGE	SEX	COLOR	LENGTH OF ILLNESS	LENGTH OF RESIDENCE IN KINGSTON	TRACHEO-BRONCHIAL LYMPH NODES		CALCIFIED PULMONARY NODULES	PLEURAL INVOLVEMENT		LUNG INVOLVEMENT				CAVITIES		SECONDARY TUBERCULOUS LESIONS IN							
						Caseous	Hyperplastic		Effusion	Adhesions*	Site of primary lesion	Caseous pneumonia	Fibrosis	Miliary	Site**	Character of walls	Pericardium	Peritoneum	Mesenteric lymph nodes	Intestines	Spleen	Liver	Kidneys	Trachea
1	9 mo.	F	DB	5 mo.	9 mo.	+				L	?			+					+		+			
2	1 yr. 10 mo.	M	DB	4 mo.	1 yr. 10 mo.	+				R–F	RL	+		+					+	+	+	+	+	
3	6 yr.	M	DB	2 mo.	6 yr.	+			100 cc. R		?			+										
4	11 yr.	F	B	5 mo.	11 yr.	+			50 cc. L	L–F R	RU	+			RU	Necrotic		+	+					
5	14 yr.	F	B	5 mo.	2 yr.	+				L–C–F R–F	RL	+									+	+		
6	14 yr.	M	DB	4 mo.	9 yr.	+				L–C–F R	LL	+			LL RU	Necrotic Necrotic		+						
7	16 yr.	M	B	10 mo.	16 yr.	+				R L	RU	+			RU RL LU	Necrotic Necrotic Necrotic								
8	17 yr.	F	DB	7 mo.	1 yr.	+				L–C–F	LU	+			LU LL	Thick Thick								
9	17 yr.	F	B	8 mo.	?	+				R L	RM	+			RM LU	Thick Necrotic			+					

10	19 yr.	F	B	7 mo.	2 yr.	+			100 cc. R	L–C–F	LL	+			LL	Necrotic		+	+	+	+	+		
11	19 yr.	F	DB	?	?	+				R	RM	+			RM RU LU	Necrotic Necrotic Necrotic								
12	20 yr.	F	DB	?	?	+				R	RU	+			RU	Necrotic								
13	22 yr.	M	B	?	?	+			1000 cc. R	L	LU	+						+			+			
14	22 yr.	M	B	7 mo.	22 yr.	+			150 cc. R	R L–F	LU	+			LU	Necrotic			+			+		
15	22 yr.	M	B	11 mo.	22 yr.	+				R	RU	+			RU RM	Necrotic Necrotic			+					+
16	24 yr.	M	B	5 mo.	5 yr.	+				L–C–F	LU	+			LU	Necrotic			+		+			
17	23 yr.	F	B	4 mo.	7 yr.	+			1500 cc. R	R L	RU	+	+				+	+	+		+			
18	25 yr.	F	B	1 yr. 1 mo.	4 yr.	+			200 cc. L	L–F	RL	+	+		RL RU	Necrotic Necrotic								
19	27 yr.	F	B	?	?	+				L	LL	+			LL LU	Thin Thin		+						
20	27 yr.	F	DB	3 mo.	6 mo.	+				R–C–F	RU	+			RU RM RL	Thin Thin Thin			+					
21	28 yr.	F	B	8 mo.	?	+				R–F	RL	+			RL RM	Necrotic		+						

* F = Fibrinous exudate and adhesions easily separated.
C = Complete obliterative pleuritis.
** First lobe mentioned constitutes site of largest cavity.

TABLE 6—*Concluded*

CASE NUMBER	AGE	SEX	COLOR	LENGTH OF ILLNESS	LENGTH OF RESIDENCE IN KINGSTON	TRACHEO-BRONCHIAL LYMPH NODES		CALCIFIED PULMONARY NODULES	PLEURAL INVOLVEMENT		LUNG INVOLVEMENT				CAVITIES		SECONDARY TUBERCULOUS LESIONS IN							
						Caseous	Hyperplastic		Effusion	Adhesions*	Site of primary lesion	Caseous pneumonia	Fibrosis	Miliary	Site**	Character of walls	Pericardium	Peritoneum	Mesenteric lymph nodes	Intestines	Spleen	Liver	Kidneys	Trachea
22	29 yr.	M	DB	1 yr. 3 mo.	?	+				L–C R	LU	+	+		LU	Thin		+	+	+	+	+		
23	34 yr.	F	B	1 yr.	11 yr.	+				R L	RU	+	+		RU LU	Thick Thin	+		+	+				
24	37 yr.	M	B	?	37 yr.	+				R–C–F	RU	+			RU	Necrotic								
25	47 yr.	M	B	6 mo.	4 yr.	+				L–C	LU	+			LU LL	Necrotic Necrotic								
26	26 yr.	M	B	?	?	+				R	LL		+					+			+	+		
27	16 yr.	F	DB	5 mo.	16 yr.	+				L	LL	+			LL	Thin								
28	18 yr.	F	B	1 yr. 4 mo.	3 mo.		+			L	LL	+	+		LL	Thick								
29	18 yr.	F	DB	?	?		+			R–C L–F	RL	+							+	+	+			
30	22 yr.	M	DB	?	?		+			L R	LL	+			LL RU	Thin Thin								
31	25 yr.	F	DB	6 mo.	4 yr.		+			R	RU	+			RU LU	Necrotic Necrotic								

32	16 yr.	M	DB	4 mo.	16 yr.		+		100 cc. L	L–F	LU	+			LU RU	Thick Necrotic			+		+			
33	33 yr.	M	B	9 mo.	?		+			R	RU	+			RU LU	Thick Thin								
34	15 yr.	F	B	2 yr. 6 mo.	5 yr.	+		+		R L	RU	+	+		RU LU	Thick Thin								
35	25 yr.	M	DB	8 mo.	6 yr.	+		+		R L–F	LU	+			LU LL RU	Thick Thick Necrotic			+	+				
36	30 yr.	M	B	1 yr. 6 mo.	7 yr.	+		+		L–C	LU	+	+		LU	Thick								
37	31 yr.	M	DB	?	?	+		+		R–F	RU	+			RU RL	Necrotic Necrotic								

* F = Fibrinous exudate and adhesions easily separated.
C = Complete obliterative pleuritis.
** First lobe mentioned constitutes site of largest cavity

fied lesions could be detected in the tracheobronchial lymph nodes or lung tissue (table 7a); there was, however, an absence of caseation or hyperplasia of the lymph nodes. The average age for this special group of 25 cases was 32.2 years; the average duration of illness 14.9 months; the average length of residence in Kingston 14.7 years. The remaining 51 cases presented the classical features of adult type pulmonary tuberculosis associated with lung involvement, either calcified tracheobronchial lymph nodes, in 4 instances, or calcified pulmonary nodules, in 27 instances, or both in combination, in 20 instances (table 7b). The average age for this group of 51 cases was 32.5 years; the average duration of illness 15.5 months; the average length of residence in Kingston 16.1 years. For the entire group of 76 cases of adult type pulmonary tuberculosis (table 1) the average age was 32.4 years; average duration of illness 15.3 months; average length of residence in Kingston 15.6 years.

The type and distribution of pleural involvement are shown in tables 2, 7a and 7b.

By definition, adult type pulmonary tuberculosis characteristically arises in one of the upper lobes, in the majority of instances. In this series the disease appeared to originate in the right upper lobe 37 times, the left upper lobe 38 times, and once in the right lower lobe. In the last case there were found definite calcified pulmonary nodules in the right lower lobe and a small calcified mesenteric lymph node near the caecum.

Cavities were found in 74 of the 76 cases of adult type pulmonary tuberculosis; the cavities were of a considerable size. Single cavities occurred in 26 instances; in 9 cases multiple cavities were confined to one side and in 39 instances they were bilateral (tables 3, 7a and 7b).

As would be expected in the more chronic type of pulmonary tuberculosis, in the majority of cases the walls of these cavities showed more extensive organization; thick fibrotic walls were found in 43 instances; thin, smooth walls in 28 instances; and rough, irregular, necrotic walls in 10 instances. There was also found a definite association between the degree of organization of the cavity walls and the duration of the disease. The average duration of the disease in patients with thick walls was 16.7 months; thin walls, 17.6 months; and irregular necrotic walls, 9.3 months.

The character of the pulmonary involvement in tuberculosis is usually influenced by the chronicity of the disease. In this series of adult type

pulmonary tuberculosis, fibrous tissue formation predominated in 32 instances; fibrosis, associated with caseous infiltration, was found in 35 instances; and in 9 instances the pulmonary lesions were almost exclusively caseous. The type of infiltration may also have a relation to the duration of the disease; in cases with chronic caseating lesions, this was found to be 5.1 months; in cases with involvement of the fibrocaseous type, 14.7 months; and in cases in which the local tissue reaction was predominantly fibrous tissue formation, 18.7 months (table 3).

Secondary involvement of other organs was not particularly striking in this series of adult type pulmonary tuberculosis. The frequency of such distributions is shown in table 4.

In none of the cases in this study of 113 autopsies was an attempt made to determine the occurrence of cerebral-spinal lesions.

DISCUSSION

This paper reports the character of tuberculous lesions found at autopsy in 113 Negroes dying of pulmonary tuberculosis in Jamaica, British West Indies. The acute character, as well as the short duration of pulmonary tuberculosis, has been reported by Opie and Isaacs (3). Also, the anatomical characteristics of tuberculosis in Jamaica have been described by Opie (2) in a review of 9 cases among adults. These reports manifest the frequent occurrence among Negroes of a type of progressive pulmonary tuberculosis designated as childhood type.

The frequency of childhood type pulmonary tuberculosis is determined by the opportunities for first infection of a massive character by persons lacking protection through previous exposure and infection. Such conditions are prevalent in Jamaica. The exposure rate to active and infectious tuberculosis in the rural parts of Jamaica is considerably lower than that found in Kingston. Many noninfected young adults migrate from the country to the city in search of employment and, for economic reasons, live in those sections where the highest frequency of tuberculosis occurs. Economic and living conditions not only influence the type of disease but also undoubtedly affect its course.

This series of 113 autopsies includes 37 classified as progressive pulmonary tuberculosis of childhood type, 32.7 per cent of the entire series. A review of 1,032 cases of pulmonary tuberculosis in Negroes observed at the Kingston Tuberculosis Dispensary during 1931 to 1934 showed 28.9 per cent diagnosed as clinical childhood type tuberculosis. In practically all of these cases the diagnosis was determined by X-ray

TABLE 7A

Adult type pulmonary tuberculosis among persons with no demonstrable lesions of childhood type

CASE NUMBER	AGE	COLOR	SEX	LENGTH OF ILLNESS	LENGTH OF RESIDENCE IN KINGSTON	CALIFIED TRACHEO-BRONCHIAL LYMPH NODES	CALCIFIED PULMONARY NODULES	PLEURISY WITH EFFUSION	PLEURITIC ADHESIONS*	SITE OF MAJOR LUNG LESION	CASEOUS TUBERCULOUS PNEUMONIA	PULMONARY FIBROSIS	CAVITIES		SECONDARY TUBERCULOUS LESIONS IN					
													Site**	Character of walls	Pericardium	Peritoneum	Mesenteric lymph nodes	Intestines	Spleen	Liver
	years				*years*															
38	15	B	F	8 mo.	2				L R	RU	+		RU	Thin		2000 cc.		+		
39	22	B	M	?	?				L	LU		+	LU LL RU	Thick Thick Thick			+			
40	23	DB	F	4 mo.	3				R	RU	+									+
41	24	DB	F	?	17				L	LU	+		LU	Thin						
42	24	B	M	1 yr. 6 mo.	9			2000 cc. R	L–C	LU	+	+	LU RU RL	Thick Thin Thin			+	+		
43	24	DB	M	2 yr. 3 mo.	12			150 cc. R 250 cc. L	L R	LU	+	+	LU RU	Thick Necrotic						
44	26	DB	F	5	1			50 cc. L	R–C	RU	+	+	RU	Thin		500 cc.	+			+
45	26	B	F	1 yr. 9 mo.	4				L R	LU		+	LU RU	Thick Thick	100 cc.	+				
46	27	DB	F	1 yr.	?			200 cc. R	L R	LU	+	+	LU	Thick						
47	27	DB	F	6 mo.	?			1500 cc. L	L R	RU		+	RU RL	Thick Thick						
48	28	DB	M	1 yr. 9 mo.	10				R–C L	RU		+	RU	Thick						

49	29	B	M	11 mo.	25				L	LU	+	+	LU LL RU	Thick Thick Thick					
50	30	B	F	?	?				R L	RU	+	+	RU RM RL	Thick Thick Thick	100 cc.				
51	30	B	F	5 mo.	6				R–C L–C	LU		+	LU RU	Thick Thick				+	
52	30	B	F	4 mo.	8				L–C R–C	RU	+	+	RU LU	Thin Thin	+				
53	33	B	F	4 mo.	30				R	RU	+		RU	Necrotic					
54	34	B	M	1 yr. 11 mo.	18				L R–F	LU	+	+	LU RU	Thick Thick					
55	34	DB	F	4 mo.	10				L	LU	+	+	LU LL RU	Necrotic Necrotic Necrotic					
56	35	B	M	8 mo.	30			250 cc. L	L	RU	+	+	RU LU	Thick Thick					
57	35	DB	F	1 yr. 9 mo.	6				R L	RU		+	RU LU	Thick Thick					
58	39	DB	M	1 yr. 2 mo.	26			150 cc. L	R–C	RU	+	+	RU LU	Thick Thick					
59	40	B	F	1 yr. 6 mo.	16			500 cc. L	R–C L	RU		+	RU RL LU	Thick Thick Thick		1500 cc.			
60	41	B	F	8 mo.	41			50 cc. L	R–C	RU		+	RU RL	Thick Thick	100 cc.	500 cc.		+	
61	60	B	M	6 mo.	5				R–C L	RU	+		RU	Necrotic					
62	70	DB	M	2 yr.	30				R L	LU		+	LU RU	Thick Thick					

* F = Fibrinous exudate and adhesions easily separated.
C = Complete obliterative pleuritis.
** First lobe mentioned constitutes site of largest cavity.

TABLE 7B

Adult type pulmonary tuberculosis among persons with demonstrable lesions of childhood type

CASE NUMBER	AGE	COLOR	SEX	LENGTH OF ILLNESS	LENGTH OF RESIDENCE IN KINGSTON	CALCIFIED TRACHEO-BRONCHIAL LYMPH NODES	CALCIFIED PULMONARY NODULES	PLEURISY WITH EFFUSION	PLEURITIC ADHESIONS*	SITE OF MAJOR LUNG LESION	CASEOUS TUBERCULOUS PNEUMONIA	PULMONARY FIBROSIS	CAVITIES		SECONDARY TUBERCULOUS LESIONS IN						
													Site**	Character of walls	Pericardium	Peritoneum	Mesenteric lymph nodes	Intestines	Spleen	Liver	Trachea
	years																				
63	12	B	F	3 mo.	12 yr.		+		R	RL	+	+	RL	Necrotic	100 cc.						
64	16	B	M	7 mo.	16 yr.	+	+		R–C L	RU	+		RU LU	Thin Thin							
65	17	B	M	7 mo.	11 yr.	+	+		L R	LU	+	+	LU RU LL	Thick Thick Thick							
66	18	B	F	4 yr.	17 yr.	+	+	250 cc. R	R	RU	+	+	RU LU	Thin Thin							
67	19	B	M	4 mo.	15 yr.	+	+		R–C	RU	+		RU	Necrotic					+	+	
68	19	B	M	7 mo.	19 yr.	+	++		L–C R	LU	+	+	LU RU	Thin Thin							
69	20	B	F	3 mo.	5 yr.		+		L R	LU	+	+	LU RU	Thin Thin							
70	20	B	F	5 mo.	7 mo.	+		500 cc. L	R–F L–F	RU	+				75 cc.		+	+	+	+	
71	20	B	F	8 mo.	1 yr.	+	+		R–C L–C	RU		+	RU LU	Thin Thin							
72	21	B	M	8 mo.	16 yr.		+	1000 cc. R	L–C	LU		+	LU	Thick							
73	22	B	M	9 mo.	?	+	+		R L	RU	+	+	RU RL LU	Thin Thin Thin							

74	23	B	M	1 yr.	7 yr.	+	+		L R	LU		+	LU RU	Thick Thick	100 cc.		+	+			
75	24	B	F	6 mo.	9 yr.		+		L R	LU	+	+	LU LL	Thin Thin							
76	24	B	F	3 mo.	8 yr.		+		L	LU	+		LU	Thin	+						
77	24	DB	F	6 mo.	6 yr.		+		L–C	LU		+	LU	Thin							
78	24	DB	M	3 yr. 3 mo.	4 yr.		+		L R	LU		+	LU RU	Thick Thick							
79	24	B	M	10 mo.	5 yr.		+		L R	LU		+	LU RU	Thick Thick			+	+			+
80	26	DB	F	2 yr. 4 mo.	8 yr.		++		L–C R	LU		+	LU RU	Thick Thin							
81	28	B	F	1 yr.	1 yr. 6 mo.	+	+		R L	RU	+	+	RU RL	Thin Necrotic							
82	28	B	M	?	?	+			L R	RU	+	+	RU RM RL	Thick Thick Thick							
83	28	DB	M	4 yr.	28 yr.	+	+		R L	LU		+	LU RU	Thick Thick							
84	29	DB	M	2 yr. 8 mo.	10 yr.		+	100 cc. R	L	RU		+	RU	Thick							
85	29	B	F	1 yr.	11 yr.	+			L R	RU	+	+	RU RL LU	Thick Thick Thick							
86	30	B	F	1 yr. 1 mo.	4 yr.		+		R	RU	+	+	RU	Thin							
87	30	DB	F	2 yr. 2 mo.	10 yr.	+			R L	LU	+	+	LU	Thin							

* F = Fibrinous exudate and adhesions easily separated.
C = Complete obliterative pleuritis.
** First lobe mentioned constitutes site of largest cavity.

TABLE 7B—*Concluded*

CASE NUMBER	AGE	COLOR	SEX	LENGTH OF ILLNESS	LENGTH OF RESIDENCE IN KINGSTON	CALCIFIED TRACHEO-BRONCHIAL LYMPH NODES	CALCIFIED PULMONARY NODULES	PLEURISY WITH EFFUSION	PLEURITIC ADHESIONS*	SITE OF MAJOR LUNG LESION	CASEOUS TUBERCULOUS PNEUMONIA	PULMONARY FIBROSIS	CAVITIES		SECONDARY TUBERCULOUS LESIONS IN						
													Site**	Character of walls	Pericardium	Peritoneum	Mesenteric lymph nodes	Intestines	Spleen	Liver	Trachea
	years																				
88	30	B	F	11 mo.	17 yr.	+	+		R–C L–C	RU		+	RU LU	Thick Thick			+		+		
89	30	DB	M	4 mo.	12 yr.	+	+		L	LU	+	+	LU LL	Necrotic Necrotic						+	
90	31	B	M	6 yr.	30 yr.	+	++		L R	LU		+	LU RU	Thin Thin							
91	31	B	M	9 mo.	25 yr.		+	100 cc. R	R L	RU	+	+	RU	Thick							
92	32	DB	M	?	?		+		L–F R	RU		+	RM RU LU	Thin Thin Thin							
93	32	DB	M	?	?	+	+		L	LU		+	LU	Thin							
94	34	DB	M	4 mo.	?		+		L–C	LU	+	+	LU	Thin							
95	35	B	F	3 yr.	?	+	+	2500 cc. L	L R	RU	+	+	RU	Thick							
96	35	B	M	1 yr. 3 mo.	35 yr.		+		R	RU		+	RU	Thin			+				
97	37	DB	F	1 yr. 1 mo.	11 yr.	+	+		R–C L	RU	+	+	RU	Thick				+			
98	38	DB	M	?	?		+		L R	LU	+	+	LU RU	Thick Thin	+						
99	39	B	M	1 yr. 4 mo.	34 yr.		+		L R	LU	+	+	LU RU	Thick Thick	+						

100	39	B	M	4 mo.	39 yr.		+	50 cc. L	R–C L	LU	+	+	LU LL	Thick Thick	+					
101	40	B	F	11 mo.	20 yr.	+	+	200 cc. L		RU		+	RU LU	Thick Thick						
102	40	DB	F	8 mo.	4 yr.		+	50 cc. L	L R–C	RU		+	RU LU	Thick Thick		100 cc.			+	+
103	40	DB	F	1 yr. 2 mo.	2 mo.		+	100 cc. L	L R	LU		+	LU	Thick			+	+		
104	44	B	M	1 yr. 3 mo.	?	+	+		L	LU		+	LU	Thick						
105	45	B	M	1 yr. 5 mo.	45 yr.		+		R–C L–C	RU	+	+	RU LU	Thick Necrotic	+					
106	47	DB	M	3 yr.	47 yr.		+		R–C L	RU		+	RU	Thick						
107	51	B	M	1 yr.	21 yr.		+		L R	LU	+	+	LU LL	Thin Necrotic						
108	54	B	M	7 mo.	32 yr.	+	+		L R–F	LU		+	LU	Thick		1000 cc.		+		+
109	54	DB	M	?	?	+	+		R L	LU	+	+	LU RU	Thin Thin						
110	55	DB	F	?	?		+		L R	RU		+	RU	Thin						
111	50	B	F	1 yr. 2 mo.	5 yr.		+		L–C R–C	LU		+	LU RU	Thick Thick						
112	40	DB	M	6 mo.	40 yr.		+		R–C L	LU		+	LU LL RU	Thick Thick Thick						
113	80	DB	M	?	?		+		R L	RU	+	+	RU LU	Thin Thin						

* F = Fibrinous exudate and adhesions easily separated.
C = Complete obliterative pleuritis.
** First lobe mentioned constitutes site of largest cavity.

examination. The proportion of childhood type pulmonary tuberculosis in any group of patients will be influenced by many factors, even though that of race remains constant. Whatever these factors may be, that of greatest importance is the opportunity which has occurred for previous infection and this, naturally, will be less for persons who have recently come to the city. These conditions held for many cases of tuberculosis encountered in Kingston.

Complete clinical history could not be obtained in a certain proportion of cases in this series. In those cases in which the information was available, rather interesting comparative data were obtained concerning childhood and adult types of pulmonary tuberculosis with respect to the average age at death. Table 5 shows the distribution of cases of tuberculosis of childhood type by age groups at death. The decrease in the proportion of cases of childhood type with advancing age is to be expected. The interesting feature is the fact that these cases occurred so late in life.

Duration of illness in the childhood type group varied from two months to two years and six months, with an average of 8.5 months; while for the adult group this varied from three months to six years, with an average of 15.3 months. The findings in the former group are comparable with those reported by Opie (2). It is significant that 61 patients with adult type tuberculosis had lived in Kingston for an average of 15.6 years, thus offering greater opportunity for previous exposure to infection; and 19 cases classed as childhood type in persons over fifteen years of age had lived in the city an average of only 9.8 years. It is probably not exceptional for a person living in a city to escape infection for years, although undoubtedly in the majority of instances this would not occur.

The cases of childhood type pulmonary tuberculosis in this series include 4 having caseous tracheobronchial lymph nodes associated with small calcified pulmonary nodules, and 6 additional cases in which caseation in lymph nodes could not be detected microscopically although the nodes were several times normal size and definitely hyperplastic. It is felt that these cases may be included in the childhood type group. Opie (2) reports 2 cases in which the adjacent lymph nodes have undergone hyperplasia, with some inconspicuous caseation; these he has designated transitional types. Both of these cases showed encapsulated caseous foci either in the lung substance or lymph nodes. Opie suggests the possibility that these encapsulated lesions developed shortly before,

or perhaps simultaneously with, the progressive pulmonary disease that caused death. The same explanation might apply to the 10 cases in this series mentioned above.

The group of adult type pulmonary tuberculosis included 25 cases in which no calcified lesions could be discovered in the lymph nodes or lung tissue. In these cases there was an absence of caseation or hyperplasia of the lymph nodes. Calcified lesions may escape detection because of their small size or because they are obscured by dense superimposing or surrounding infiltrative processes in the lung. All of the cases in this group except one showed moderate to extensive cavitation. It is not improbable that in some instances excavation may involve that portion of lung which was the site of the primary infection, and that the loss of lung tissue might embrace the calcified lesion, thus accounting for its disappearance.

In Negroes of Philadelphia, Everett (4) found evidence of first infection (calcified lesion) in only 15 of 22 cases of adult type tuberculosis, a proportion practically identical with that obtained in this series.

Involvement of the pleura occurred in all but 2 of the 113 cases in the series. The character of the pleural involvement differed in some degree in relationship to the type of the pulmonary disease. In 16 (43.2 per cent) of the cases of childhood type tuberculosis the involvement was largely fibrinous, with or without fluid, compared to 5.3 per cent similar involvement in the cases of adult type tuberculosis. The significance of this difference is shown by $\chi^2 = 24.6$; $P = 0.000$. This fibrinous type of reaction seemed to be related to the shorter duration of illness. In 13 cases of childhood type, where the information was available, the average length of illness was 6.2 months, and for 3 adult type cases, 11.7 months. On the other hand, dense fibrous adhesions occurred more frequently in adult type tuberculosis. Seventy-one (93.4 per cent) were of this type, compared to 20 (54.1 per cent) in the childhood type tuberculosis. That this difference is significant is further shown by $\chi^2 = 24.6$; $P = 0.000$. Here again there was a relationship between the nature of the pleuritic involvement and the duration of illness. Childhood type tuberculosis with such pleuritic involvement averaged 11.1 months in duration of illness and the adult type cases 15.5 months.

Autopsy reports on findings in Negroes dying from pulmonary tuberculosis contain little with reference to the extent of pleural involvement. Pirie and Mavrogordato (5) report pleurisy occurring in 89 (36.9 per cent) of 241 thoracic type cases of tuberculosis in South African natives.

Everett (4) does not discuss the frequency of pleural involvement, but search through the protocols of his Negro cases discloses reference to pleuritic involvement in 50 per cent of adult type tuberculosis and in 13.6 per cent of his childhood type cases.

A number of references to pleuritic involvement in white patients are available, the frequency varying from 42.4 per cent (6) in Glasgow to 100 per cent (7) in California. Opie (2) writes, "The well-known characteristics of pulmonary tuberculosis of young children are as follows: The lesion may have its origin in any part of the lung substance and is not more frequently situated in the apex than elsewhere . . . in the later period of childhood and in adult life tuberculosis of white persons (*adult type*) assumes a different character. The lesion has its origin at the apex of the lung; . . . progressive type of childhood usually pursues an acute course, there is in most instances little formation of fibrous tissue . . . and cavity formation is much less common than in adults . . . with progressive pulmonary tuberculosis of adults fibrosis and cavity formation are rarely absent." In the same reference Opie reports 8 cases, 6 childhood tuberculosis and 2 transitional forms, in 5 of which the disease had its origin in a lower lobe; in the remaining 3 cases the origin was in an upper lobe. Everett (4) reports pathological findings in 22 cases of childhood tuberculosis and an equal number of adult type tuberculosis in Negroes. In the childhood type the disease had its origin in an upper lobe in 13 instances; in the remaining 9 cases it originated in a lower lobe. In 35 cases of childhood type, 21 (60 per cent) occurred in an upper lobe; the remaining 14 occurred in one of the lower lobes. Two cases of miliary tuberculosis failed to show any evidence of the origin of the disease. In 76 cases of adult type, 75 arose in an upper lobe. These findings agree closely with the classical characteristics described above. In a large proportion of the cases of progressive tuberculosis of childhood type, caseous or fibrocaseous tissue reactions predominated in 34 out of 37 cases (91.9 per cent). In the adult type tuberculosis only 57.9 per cent showed similar reactions and in the latter group the fibrocaseous reaction predominated. The difference in the frequency of occurrence of this type of reaction between childhood and adult types is definitely significant, $\chi^2 = 13.5$; $P = 0.000$. Fibrous tissue formation occurred seldom in the cases of childhood type tuberculosis—in this series, once. This type of tissue reaction, however, predominated in 32 instances in the adult group. Everett (4) found a

similar difference but a more frequent occurrence of fibrous tissue formation in his childhood group.

According to Opie (2), cavity formation is much less common in the childhood type of tuberculosis. Everett reports that cavities were found in 18 of 22 cases of childhood type, and in every instance in 22 cases of adult type of the disease. In the present series cavities were found in 29 out of 37 cases of childhood type tuberculosis (78.4 per cent) and in 74 out of 76 cases of adult type (97.4 per cent). This difference is definitely significant, $\chi^2 = 11.1$; $P = 0.001$. In the childhood group cavity formation occurred most frequently in an upper lobe (19 instances), and only 10 times in a lower lobe. On the other hand, in the adult type tuberculosis group the principal cavity formation occurred in an upper lobe in 72 of the 74 cases having cavities. The character of the wall formation of cavities differed somewhat in the two groups of cases. Thick, organized, smooth-walled cavities predominated in the adult type tuberculosis group, while ragged, necrotic, caseous walls were more frequent in the childhood type tuberculosis group. In both groups there was a definite relationship between the duration of the disease and the character of the walls of the cavities, death occurring in a shorter time in those cases having necrotic and unorganized cavity walls.

The frequency of extrapulmonary lesions in tuberculosis in Negroes varies somewhat in the reports of other writers. Everett (4) has little to say concerning such lesions, but mentions the occurrence of tuberculous peritonitis in 5 of his 22 cases of childhood tuberculosis and once in 22 cases of adult tuberculosis. Harvey, Pirie and Mavrogordato (5) in 241 cases of thoracic type report the frequency of secondary tuberculous lesions in the following organs and tissues: pericardium, 54 (22.4 per cent); spleen, 174 (72.2 per cent); liver, 145 (60.2 per cent); kidneys, 73 (30.3 per cent); intestines, 59 (24.5 per cent); peritoneum, 56 (23.2 per cent); and mesenteric lymph nodes, 111 (46.1 per cent). No distinction is made between childhood and adult type tuberculosis in the above figures. The impression one obtains, however, is that these cases were largely childhood type tuberculosis. In our series of 37 childhood and 76 adult cases of tuberculosis in Negroes, extrapulmonary lesions were found more frequently in the progressive pulmonary type of childhood tuberculosis (table 4) than in the adult type. The differences in frequency were found significant, however, only in the occur-

rence of caseous mesenteric lymph nodes and tuberculous lesions in the spleen, and possibly in those involving the peritoneum.

SUMMARY

1. Autopsy findings are reported for 113 Negroes dying of pulmonary tuberculosis in Jamaica, classified as 37 cases of progressive childhood type and 76 cases of adult type.

2. The average age, duration of illness and length of urban residence were materially less in those cases designated as childhood type tuberculosis.

3. Pleuritic involvement was present in a large proportion of cases and with about equal frequency in both groups.

4. The disease originated in one of the upper lobes in 60 per cent of the childhood type group and in 98.7 per cent of the adult type group.

5. Cavity formation occurred most frequently in one of the upper lobes in both adult and childhood types.

6. In childhood type tuberculosis caseous pneumonia was the predominant pulmonary tissue reaction; while in the adult type the most frequent and characteristic tissue reaction was fibrous tissue formation.

7. Extrapulmonary lesions secondary to the pulmonary disease occurred in both groups of cases, but more frequently in those cases designated as progressive childhood type tuberculosis.

REFERENCES

(1) Diagnostic Standards, Tuberculosis of the lungs and related lymph nodes, Natl. Tuberc. A., New York, 1938.
(2) Opie, E. L.: J. Exper. Med., 1917, *25*, 855; 1917, *26*, 263.
(3) Opie, E. L., and Isaacs, E. J.: J. Hyg., 1930, *12*, 1.
(4) Everett, F. R.: Am. Rev. Tuberc., 1933, *27*, 411.
(5) Pirie, J. H. H., and Mavrogordato, A.: South African Inst. Med. Res. Pubs., Johannesburg, no. 30, 1932.
(6) Blacklock, J. W. S.: Spec. Report Series, Brit. Med. Res. Coun., London, no. 172, 1932.
(7) Sanders, A. O.: Am. Rev. Tuberc., 1929, *20*, 128.

CASE REPORTS

ANTHRACOSILICOSIS SIMULATING PULMONARY CARCINOMA[1]

With Report of a Case

HOWARD H. BRADSHAW AND RICHARD J. CHODOFF

Thoracic surgery has made such tremendous advances in recent years that exploratory thoracotomy is no longer considered a "last hope" procedure in the study and treatment of obscure thoracic lesions. Its place in the fight against pulmonary carcinoma is recognized. Certainly one should not hesitate to recommend exploration in those cases in which the diagnosis remains in doubt after conservative measures have failed. Examples in which even exploration of the thorax fails to make a correct diagnosis are fortunately rare. However, they occur. Overholt (1) reports a case in which the diagnosis of pulmonary neoplasm was made on the basis of X-ray shadows and symptoms of cough, haemoptysis and loss of weight. At operation it was felt that the lung was the site of a malignant lesion and pneumonectomy was carried out. Examination of the specimen proved the lesion to have been a circumscribed lung abscess. Overholt stresses the fact that even palpation of the lung at operation may leave the diagnosis in doubt. His opinion, with which we agree, is that lobectomy or pneumonectomy may prove to be the safest procedure in these cases.

Recently we had under our observation a patient presenting symptoms and radiological evidence that seemed typical of pulmonary carcinoma. There was also a long history of exposure to coal dusts. At operation the diagnosis of pulmonary carcinoma was made and a total pneumonectomy performed. The lesion proved to be anthracosilicosis. The case is reported here in detail.

Case Report

W. W., male, age 34, was admitted to Jefferson Hospital on December 3, 1936, complaining of cough, expectoration, loss of weight and shortness of breath for the past nine months. The past history was irrelevant except

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for the occupational history. At the age of thirteen he began working in the coal mines, continuing intermittently for four years. Following this he spent one year in a viscose mill. The subsequent six years he worked in a railroad roundhouse, in an atmosphere full of soft coal smoke. He then spent a year as a rock driller in an anthracite mine; leaving this job, he worked as a gas station attendant up to the time of illness. When first taken sick he was admitted to Williamsport, Pennsylvania Hospital. His sputum was repeatedly negative for tubercle bacilli. An X-ray film of the chest taken here was reported as follows: "Left diaphragm smooth, right pulled up by adhesions. Area of dense clouding about size of half dollar at right hilum fading out into normal lung. Below and somewhat external to this is another smaller area of feathery clouding. This resembles lung abscess but a positive diagnosis cannot be made by X-ray. A bronchogenic neoplasm or mass of tuberculous hilar nodes cannot be ruled out. Left lung is negative."

No diagnosis could be made and he was referred to Jefferson Hospital for further study. On December 3, 1936, bronchoscopy was performed by Dr. L. Clerf, who reported "some bleeding from the right lower lobe bronchus. There is distortion of the right middle lobe bronchus but nothing was noted to suggest neoplasm nor was there sufficient secretion observed to suggest abscess."

An X-ray film taken on December 4, 1936 was reported as follows: "The chest shows a density close to the right root area extending up toward the upper lobe. It is fairly well circumscribed but there is some radiation into the surrounding tissues. It is suggestive of a malignant lesion. There are increased pulmonary markings in the right lower lobe, otherwise the lungs have a normal appearance. Slight displacement of the trachea to the right." (Figure 1.)

Sputum examinations were repeatedly negative for tubercle bacilli. On December 12, 1936 Doctor Clerf reported that from the bronchoscopic examination "there is undoubted obstruction to the right upper lobe bronchus. Tendency for the mucosa to bleed." Iodized oil was instilled bronchoscopically on December 14, 1936 and a bronchogram taken. The report was: "Close to the orifice of the right upper lobe bronchus the oil has collected in several small pools and also has scattered in an irregular fashion in the lung

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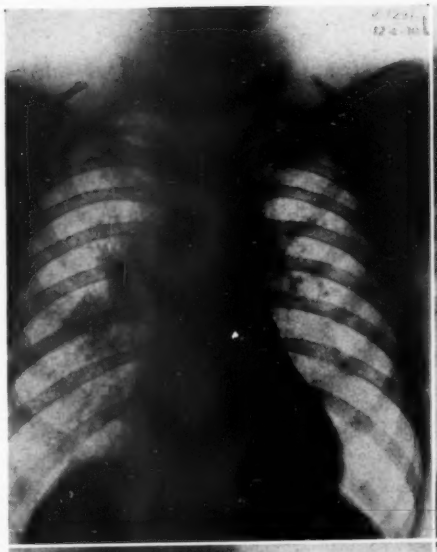
FIG. 1. X-ray film taken on December 4, 1936. A circumscribed area of density is seen at the right root area.

FIG. 2. X-ray film taken on December 14, 1936, after bronchoscopic instillation of iodized oil. Pooling of the oil in the right root area shows evidence of destruction of lung tissue.

FIG. 3. Lateral X-ray film of chest taken on December 23, 1936.

FIG. 4. X-ray film taken on May 5, 1938, after two courses of roentgen therapy. Upward retraction of hila is seen.

FIG. 5. Lateral view taken on May 5, 1938.



IG. 1

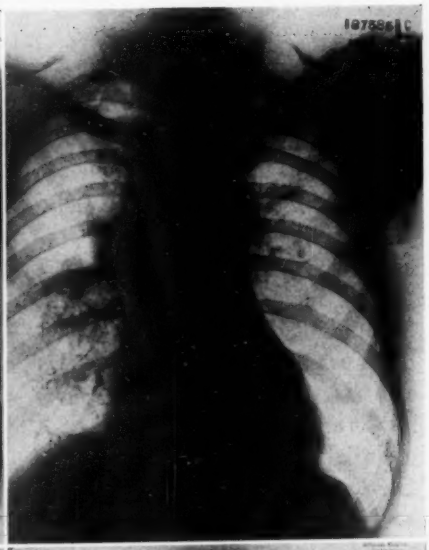


FIG. 2

FIG. 3

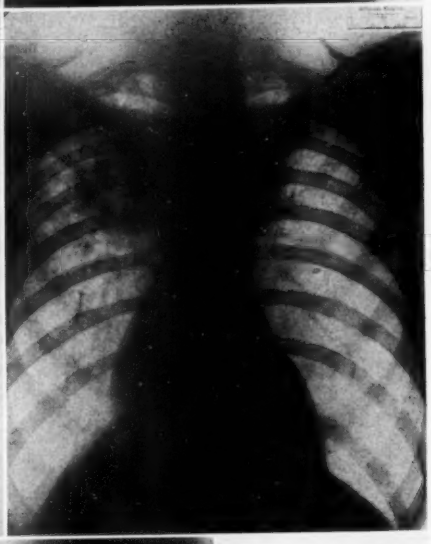


FIG. 4

FIG. 5

tissue about it. Part of the bronchial tree is outlined, having a normal appearance. The manner of collection of the oil suggests possible abscess formation or destruction of the lung tissue by some pathological process." (Figure 2.) A film of the chest, made on December 17, 1936, at the end of expiration, showed that "the right lower lobe empties well but there appears to be obstructive emphysema of the right upper lobe." On December 19, 1936 bronchoscopy was repeated. The observations were: "Right upper lobe bronchus investigated. No definite evidence of growth. There is, however, something in the right upper lobe bronchus which bleeds readily when touched by forceps or aspirating tube. Material removed for examination." The material removed was reported by the laboratory as "inflammatory exudate." Further biopsy material was obtained on December 23, 1936 and reported as "blood clot and anthracotic tissue." Lateral X-ray films taken on December 23 demonstrated that the obstruction involved only the right upper lobe. (Figure 3.)

At no time during the patient's hospital stay did he have any elevation of temperature or of pulse rate. Haemoptysis did not occur. The diagnosis at this time remained in doubt. The history of exposure to dust suggested anthracosilicosis. Tuberculosis seemed unlikely in view of the nature of the X-ray films, the persistently negative sputum and the absence of fever or increased pulse rate. X-ray and bronchoscopy suggested that the most probable diagnosis was bronchogenic carcinoma, superimposed on anthracosilicosis. Exploratory thoracotomy was advised but the patient refused and returned to Williamsport on December 23, 1936.

At Williamsport, Pennsylvania Hospital on December 26, 1936 an X-ray film of the chest revealed an infiltrating mass in the hilum of the right lung which spread outward into the middle lobe and upper part of the lower lobe. This was thought to be a pulmonary carcinoma. Between January 4 and January 23, 1937 he was given a course of deep roentgen ray therapy. On February 10, 1937 a chest X-ray film presented no change in the appearance of the lesion. Subsequent films on February 22 and March 15, 1937 also showed no change. A second course of X-ray therapy was given between May 17 and June 11, 1937. On February 4, 1938 a chest X-ray film indicated that the lesion was more extensive than on previous studies.

On May 5, 1938 he was again admitted to Jefferson Hospital with a history of increasing dyspnoea, cough and expectoration. No haemoptysis had occurred. He had lost twenty-one pounds since his previous admission. An X-ray film taken the day of admission revealed: "Considerable change in chest since last plate taken on December 21, 1936. Both hila are symmetrically and markedly elevated. In addition there is an increase in the fibrosis radiating upward and laterally from both hila. The left lower lobe field is emphysematous. The trachea is displaced to the right. A moderate amount

of lipiodol remains in the right upper lobe as a result of the previous pneumonography." (Figures 4 and 5.) Bronchoscopic examination on May 7, 1938 revealed: "The trachea is displaced to the right as is the right bronchus. The right upper lobe bronchial orifice is visualized without difficulty. At the level of the middle lobe bronchus the lumen is almost obliterated, the result of an extrabronchial lesion which is producing compression. There is no abnormal secretion present nor is there any inflammatory change in the mucosa. The observations suggest an extrabronchial lesion which is producing compression stenosis with deformity of the right bronchus, beginning at the level of the middle lobe."

Diagnostic pneumothorax on the right side was attempted, but was unsuccessful, presumably due to pleural adhesions. On May 13, 1938 an aspiration biopsy was done but no cellular elements were noted in the material obtained. As on the previous admission, temperature and pulse had remained normal.

Exploratory thoracotomy was again advised and the patient consented. On May 27, 1938 Dr. Howard Bradshaw performed the operation under endotracheal cyclopropane-ether-oxygen anaesthesia. A curved scapular incision was made and the fourth and fifth ribs resected. A small amount of clear fluid was encountered on opening the pleural cavity. A dense, broad adhesion was present between the apex of the right lung and the anterolateral chest wall. A few other adhesions were present. When the lung was freed a large mass was felt in its upper portion. It was stony hard and the pleural surface overlying it was covered by a grayish exudate. Grossly it appeared to be a typical pulmonary carcinoma. A few small nodes were felt about the hilum of the lung and along the trachea. Total pneumonectomy was performed. The major incision was closed tightly and drainage established by means of a tube through the seventh interspace. At the end of the operation a pneumothorax was discovered on the left side. The air was at once removed. The patient was placed in an oxygen tent and the intercostal tube attached to a suction pump with 3 cm. of water negative pressure. A transfusion of citrated blood was given and continuous intravenous glucose-saline started. Pneumothorax recurred on the left side and the patient died as the air was being withdrawn.

The pathological report of the excised lung by Dr. Baxter Crawford follows: "The pleural surface of the lung is thickened and ragged. The entire lung contains much black pigment and the upper three-quarters of the upper lobe is solid and nodular. On section this is composed of dense, consolidated black tissue. Small areas have broken down. The remainder of the lung contains a moderate amount of pigmentation and of fibrotic foci."

Histology: The lung parenchyma in the consolidated area is entirely replaced by dense fibrous tissue in which there is a large amount of black pig-

ment. The fibrous tissue is in the form of small nodules in areas which form hyalinized foci. In other areas the connective tissue is more cellular. Only a few atrophied bronchioles and air vesicles are observed in the tissue. At the apex there is marked thickening and fibrosis of the pleura. The small fibrotic nodules are suggestive of silicosis.

Diagnosis: Anthracosilicosis with extensive fibrosis and consolidation.

Autopsy (summary): Pulmonary anthracosis and fibrosis, localized, left apex. Chronic rheumatic endocarditis.

DISCUSSION

Whether the incidence of carcinoma of the lung is increased in pneumonoconiosis is a debatable question, although the majority of observers to-day feel that carcinoma does not occur more often in the pneumonoconiotic than in the normal lung. The often quoted example of the high incidence of pulmonary carcinoma in workers in the Schneeberg and St. Joachimstal mines is based on a misinterpretation of the facts.

According to Saupe (2) the aetiological factor in these cases is not the inorganic dust but the radioactive substances in the inhaled air. Vorwald and Karr (3) in a study of autopsies at Saranac found a percentage of pulmonary tumors of 0.074 in silicotics and of 0.014 in nonsilicotics. They quote the following figures from the miners' Phthisis Medical Bureau, South Africa:

	NUMBER OF AUTOPSIES	NUMBER OF CARCINOMA OF THE LUNG	PER CENT CARCINOMA
Miners with silicosis	1,438	10	0.70
Miners without silicosis	1,679	12	0.71
Males never underground	1,393	13	0.93

These figures indicate that pulmonary carcinoma is an unusual complication of silicosis.

In the occasional case in which carcinoma develops as a complication of pneumonoconiosis the diagnosis is difficult. The symptoms and radiological findings of the primary disease may cloud or completely obscure those of the carcinoma. It may be impossible to prove the presence of carcinoma in an individual in which it is suspected, except at autopsy. Bronchoscopy is invaluable but is not infallible. X-ray studies may be of no help, as the increased hilar shadows of advanced silicosis may be mistaken for carcinoma. Gut (4) reported a case in which X-ray observations indicated the presence of a bronchogenic carcinoma. Shadows in the other lung led to the belief that metastatic lesions were

present. At autopsy it was noted that anthracotic induration at both hila had caused bronchostenosis and obstructive emphysema.

Pancoast and Pendergrass (5) divide the X-ray findings in pneumonoconiosis into three phases:

1: The phase of perivascular, peribronchial, lymph node enlargement. X-ray films show increased linear markings and enlarged hilar shadows.
2: The phase of early interstitial fibrosis. The lungs are homogeneously hazy. The hilar shadows are increased. Small nodules may be scattered throughout the lung fields.
3: The phase of nodular coalescence and fibrosis. This is the most characteristic picture of pneumonoconiosis. Small, discrete nodules are present throughout both lungs. These may become conglomerate.

The phase of nodular coalescence as described by Pancoast and Pendergrass (5) corresponds to the end stages of lymphatic stasis, lymph node enlargement and massive fibrosis described by Gardner (6). The X-ray picture, although the increased hilar shadows may occasionally suggest carcinoma, usually shows enough of the associated features of pneumonoconiosis to make the diagnosis reasonably certain. Gardner (7) states "in silicosis the first pathognomonic shadow is that of the fine nodule in the parenchyma of the lung field . . . one is not justified in diagnosing silicosis unless he sees the characteristic nodular shadows in the lung field." We feel that this statement is misleading, since many cases of silicosis do not show the typical nodular shadows Gardner describes. Massive hilar shadows may be present and may not be accompanied by nodular shadows in the rest of the lung. Fortunately, the bilateral, symmetrical nature of these shadows in pneumonoconiosis usually serve to distinguish them from bronchogenic carcinoma, in which the shadow is usually unilateral. The difficulty sometimes encountered in differentiating pneumonoconiosis from pulmonary neoplasm is recognized by Garland (8) who states that pulmonary tumors rarely simulate pneumonoconiosis but that the converse is not infrequently seen. Large, coalescent fibrotic areas may resemble single or multiple metastatic tumors. Minet (9) and his associates have reported a roentgen study of miners whose lungs showed pseudotumoral shadows. Of these cases, only one in nine presented a single shadow. All showed evidence of emphysema and peribronchial fibrosis. The statement of Hugenin that any pulmonary shadow, regardless of shape or form, may be due to carcinoma is questioned by these observers. They believe that the multiplicity of shadows in pneumonoconiosis, as well as the long duration of the symp-

toms and the absence of haemoptysis are sufficient evidence to rule out carcinoma.

In none of the reports on the roentgenological appearance of pneumonoconiosis have we found a description of a single, enlarged hilar shadow, producing bronchostenosis and lobar emphysema and showing no evidence of nodular shadows in the rest of the lung fields. We must take exception, therefore, to Gardner's statement that one is not justified in diagnosing silicosis unless nodular shadows are seen.

SUMMARY AND CONCLUSIONS

A case is presented that illustrates the difficulty that sometimes arises in the diagnosis of intrathoracic lesions, and also emphasizes the fact that the accepted criteria for the recognition of pneumonoconiosis need some revision. The symptoms of both diseases may be very similar. True, haemoptysis is seen more often in carcinoma but the presence or absence of a single symptom cannot be made the sole basis of a diagnosis. Neither pulmonary carcinoma nor pneumonoconiosis respond to roentgen ray therapy. We believe, with Overholt, that, until the attitude of the medical profession toward exploratory thoracotomy approaches that which is current toward exploratory laparotomy, mistakes will happen. It will be only through the accumulation of experience in direct observation and palpation of pulmonary lesions that thoracic surgeons will be able to recognize pulmonary carcinoma as easily as the experienced abdominal surgeon is able to recognize, for example, carcinoma of the colon. Thoracic surgery has advanced to the point where the chest may be opened, if not with impunity, certainly with a reasonable assurance of safety.

REFERENCES

(1) Overholt, R. H.: Pneumonectomy for malignant and suppurative disease of lung, with report of 8 cases, J. Thoracic Surg., 1935, *5*, 54.

(2) Saupe: Cited by Vorwald and Karr (3).

(3) Vorwald, A. J., and Karr, J. W.: Pneumoconiosis and pulmonary carcinoma, Am. J. Path., 1938, *14*, 49.

(4) Gut, H.: Anthracosis Pulmonum, Lungentumor vortäuschend, Beitr. z. Klin. d. Tuberk., 1935, *87*, 157.

(5) Pancoast, H. K., and Pendergrass, E. P.: Roentgenologic aspect of pneumoconiosis and its differential diagnosis, J. A. M. A., 1933, *101*, 587.

(6) Gardner, L. U.: Pneumokoniosis, Internat. Clin., 1935, *2*, 16.

(7) Gardner, L. U.: Diagnosis of silicosis, with special reference to roentgenological manifestations, Ann. Int. Med., 1936, *10*, 166.

(8) Garland, L. H.: X-ray aspects of pneumoconiosis, Radiology, 1936, *27*, 21.

(9) Minet, J., Dupire, P., and Hayem, A.: Contribution a l'étude radiologique du poumon des mineurs; images pseudotumorales observées chez des mineurs de houille, Presse méd., 1934, *42*, 913.

AN UNUSUAL CASE OF TUBERCULOSIS OF THE SPINE

THEODORE T. FOX,[1] MICHAEL S. BURMAN[1] AND SAMUEL SINBERG[1]

The diagnostic criteria of tuberculosis of the spine are usually based on the late manifestations of the disease.

Ornstein and Ulmar cite a number of instances where even in advanced cases of tuberculosis of the spine the roentgenographic findings were negative. The case to be reported illustrates the difficulty of making the diagnosis when the suggestive roentgenographic evidence is that of fracture rather than that of an inflammatory process.

Case Report

F. K., a 25 year old colored male, was seen on January 27, 1937, giving a history of having sustained an injury to the spine on September 15, 1936. While carrying a crate of carrots weighing 150 pounds on his head, the patient slipped on the sidewalk and struck his back against the curbstone. The injury was sustained with the spine in extension rather than in flexion. He was able to get up and walk, but did not report to work on the following day because of pain. He consulted a private physician who treated him palliatively until November 11, 1936. Following this he went to a hospital where roentgenograms taken on November 19 showed no evidence of disease in the lumbar spine. He received symptomatic treatment with no improvement in his complaint of low back pain. Stereoscopic plates were then taken of this area (February, 1937) and the roentgenologist reported a break in the outline of the upper posterior border of the body of the third lumbar vertebra, suggesting an incomplete fracture at this site.

Our own examination indicated that there was no deformity of the spine, but that all motions of the back, especially lateral motions, were limited. There was spasm of the spinal muscles. Tenderness was present over both sacroiliac joints, over the sacrolumbar area and over the lumbar spinous processes. Our roentgenograms showed a free, roughly triangular fragment of bone, measuring 1.5 cm. in its long diameter, at the superior and posterior part of the third lumbar vertebra. It was displaced slightly upward. Although this is a rather atypical site of fracture of a lumbar vertebra, it was interpreted as an incomplete fracture (S.S.). It seemed that this part of the vertebra might have been injured by the fall in extension. He was placed in

[1] New York City.

traction on a Bradford frame at the time of his first admission to the Hospital for Joint Diseases on March 6, 1937. On March 18, a plaster of paris jacket was applied. He was relieved of his pain for the most part by the support of the jacket and later a brace and by diathermy treatments. Dull pain was sometimes present in rainy weather and on effort. There was always a slight residual muscle spasm and some limitation of motion, especially in lateral and forward flexion. The roentgenogram of August 21, 1937 indicated healing of the supposed fracture of the third lumbar vertebra. There was some narrowing of the adjacent intervertebral disc and osteoporosis of the body of the affected vertebra.

On September 8, 1937, one year after the original injury, the patient was seen at his home because of severe headache and vomiting for a period of eight days. This had been preceded by intermittent headache for two weeks, and a feeling of poor health. He was semistuporous but could be aroused to answer questions. He was then somewhat incoherent. The principal findings were a temperature of 100.4°F., nuchal rigidity, photophobia and bilateral Kernig and Brudzinski signs. He was immediately hospitalized with a diagnosis of meningitis. All deep reflexes were hyperactive. The Babinski sign was negative. A bilateral low grade papilloedema was noted. There were no tubercles seen in the fundus. Spinal tap on admission showed a clear fluid, with 173 lymphocytes per cc.

A roentgenogram of the chest on September 11, 1937 disclosed individual and conglomerate parenchymatous lobular infiltrations scattered throughout the right lung and the upper third of the left lung. This was considered to be due to a parenchymatous tuberculosis. A similar roentgenographic examination of the chest on September 20 showed that throughout both lungs there was a condition which resembled somewhat the early stage of miliary tuberculosis.

While in the hospital, the patient ran a temperature ranging from 101° to 104.2°F., the average temperature being about 102.6°F. The pulse rate was between 100 and 140, reaching 150 antemortem. The patient was markedly restless, requiring intravenous sedation by sodium amytal. He could take only fluids and vomited frequently. He was incoherent and poorly oriented. Spinal taps were done as a therapeutic measure under evipal anaesthesia. On September 19 the patient became semicomatose, developed localized muscle twitchings of the extremities and had brief spells of hiccoughing. He died on September 23, 1937.

FIGS. 1A and 1B. Anteroposterior and lateral views of the lumbar spine show area of destruction which was mistaken for fracture.

FIG. 2. The sagitally cut autopsy specimen showing the areas of caseation in the second and third lumbar vertebrae.

FIG. 3. Lateral roentgenogram of the autopsy specimen.

FIG. 1A

FIG. 1B

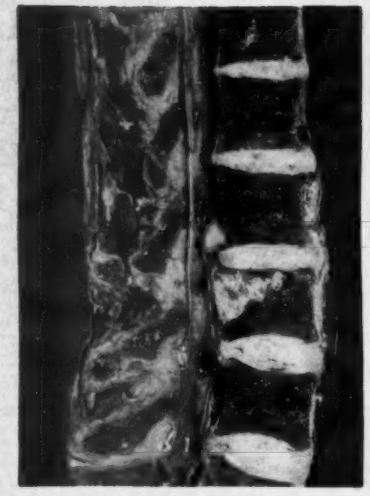


FIG. 2

FIG. 3

On account of the demonstration of tubercle bacilli in the spinal fluid of September 14, it was thought that there might exist a relationship between the trauma sustained a year before and the present clinical picture. Roentgenograms of the lumbar spine were repeated on September 18, 1937 and interpreted by Dr. M. M. Pomeranz as follows: There is no kyphosis or scoliosis. There is a slight narrowing of the intervertebral disc between the bodies of the second and third lumbar vertebrae. In the right half of the body of the third lumbar vertebra, immediately below its superior surface, an abscess cavity approximately one inch in diameter is noted. The margins of this cavity are slightly sclerotic. The anterior part of the involved vertebra shows no specific alteration. There is no collapse of the vertebra nor any significant atrophy. There is a slight bulge in the psoas muscle on the right side. Conclusion: destructive process involving the second lumbar vertebra which has not the typical appearance of a tuberculous process.

Although roentgenographic evidence was not conclusive, clinically, one felt sufficiently certain of a causal relationship between the injury and the miliary tuberculosis so that a medical examiner's necropsy was insisted upon. The following pertinent findings on postmortem examination were reported: The lungs showed no calcified lymph nodes or primary complex. Miliary tubercles were present in the liver, the adrenal glands, the spleen and kidneys. An isolated, yellowish, subintimal nodule was seen in the thoracic portion of the aorta. The dura was adherent to the pia and arachnoid and brain substance by a plastic exudate in several areas over the convexity anteriorly. The pia and arachnoid were oedematous, and studded with numerous pin-head and several somewhat larger whitish and yellowish nodules. The largest of these attained the size of tuberculomata, one measuring 0.5 cm. in diameter. Similar findings, but to a lesser degree, were observed in the region of the base of the brain. Superficially, within the substance of the left occipital lobe, two larger yellowish foci were noted, which had softened cores and appeared to be tuberculomata. One of the foci was present inferiorly and the other superiorly.

The posterosuperior part of the third lumbar vertebra was destroyed and replaced by yellowish-white, caseated material. Moderate osteosclerosis was present about this caseated area. The adjacent second lumbar vertebra showed a very small area of destruction at its posteroinferior part. The abscesses within the two bodies communicated by a narrow zone between the dura and the posterior surfaces of the bodies. The vertebral bodies were not compressed. The intervertebral disc was slightly narrowed. There were bilateral psoas abscesses. No evidence of fracture was found, old or new. A roentgenogram of the sectioned body showed no fracture line.

Microscopical examination confirmed the gross findings in all details. Of particular interest was the finding of two tubercles in a myocardial section. The intimal aortic nodule was apparently a tuberculoma. A tubercle was found in the pancreas.

This case presents two points of interest, diagnostic and medico-legal. Trauma is a frequent cause of back pain. Roentgenography is a valuable diagnostic adjunct in diseases of the spine. In this case, the interpretive ability of clinicians and roentgenologists failed and the patient was treated for fracture of the spine for one year. Where diagnosis by roentgenogram is not definite and conclusive, the possibility of an inflammatory lesion should be considered. This should have been suspected earlier in this case because of the persistence of muscle spasm and limitation of motion, in the presence of an atypical roentgenographic picture. The site of involvement was not typical for fracture nor for tuberculosis.

Since this was a compensation case, the finding of tuberculosis added a complication to the legal aspect (which, ultimately, was decided in the patient's favor).

CONCLUSION

A case is presented to demonstrate the difficulties in making a diagnosis of spinal tuberculosis, when X-ray studies are inconclusive. The diagnosis of the initial lesion was not made until the occurrence of miliary tuberculosis and tuberculous meningitis.

REFERENCES

(1) Ornstein, G. G., and Ulmar, D.: Tuberculous caries of the vertebral bodies, Quart. Bull. Sea View Hosp., 1935, *1*, 3.

(2) Pomeranz, M. M.: Am. J. Roentgenol., 1933, *29*, 753.

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